PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 295/155, A61K 31/495

A1

(11) International Publication Number: WO 95/04051

(43) International Publication Date: 9 February 1995 (09.02.95)

(21) International Application Number: PCT/GB94/01641

(22) International Filing Date: 29 July 1994 (29.07.94)

(30) Priority Data:

098,333	30 July 1993 (30.07.93)	US
169,879	17 December 1993 (17.12.93)	US

(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).

Published
With international search report.

(71) Applicant *(for all designated States except US)*: THE WELLCOME FOUNDATION LIMITED [GB/GB]; Unicorn House, 160 Euston Road, London NW1 2BP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CHANG, Kwen-Jen [US/US]; 2476 Foxwood Drive, Chapel Hill, NC 27514 (US). BISHOP, Michael, Joseph [US/US]; 235 Lochridge Drive, Durham, NC 27713 (US). BUBACZ, Dulce, Garrido [DO/US]; 114 Abbott Lane, Cary, NC 27513 (US). MC NUTT, Robert, Walton, Jr. [US/US]; Apartment B-9, 700 Morreene Road, Durham, NC 27705 (US).

(74) Agent: STOTT, Michael, John; The Wellcome Foundation Limited, Langley Court, Beckenham, Kent BR3 3BS (GB).

(54) Title: PIPERAZINE COMPOUNDS USED IN THERAPY

(57) Abstract

Diarylmethyl piperazine compounds are disclosed having utility as exogenous receptor combinant species for binding with receptors such as delta, mu, sigma, and/or kappa receptors. Compounds of the invention may be employed as conjugates in agonist/antagonist pairs for transductional monitoring and assays of neurotransmitter function, and also variously exhibit therapeutic utility, including mediating analgesia, and possessing utility for the treatment of diarrhea, urinary incontinence, mental illness, drug and alcohol addiction/overdose, lung edema, depression, asthma, emphysema, and apnea, cognitive disorders, and gastrointestinal disorders.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

PIPERAZINE COMPOUNDS USED IN THERAPY.

This invention relates generally to diarylmethyl piperazine compounds having utility in medical therapy especially as receptor-binding species, e.g., as conjugates in agonist/antagonist pairs for verifying/assaying receptor and neurotransmitter function. The compounds of the invention include benzhydryl piperazine compounds useful as mu and/or delta receptor opioid compounds mediating analgesia, as well as compounds having utility in treatment of pain, combatting drug addiction, alcohol addiction, drug overdose, mental illness, urinary incontinence, cough, lung edema, diarrhea, depression, and cognitive, respiratory, and gastro-intestinal disorders. The invention also relates to pharmaceutical formulations of such compounds, methods of treating certain disorders with such compounds, and processes by which such compounds may be prepared.

In the study of opioid biochemistry, a variety of endogenous opioid compounds and non-endogenous opioid compounds has been identified. In this effort, significant research has been focused on understanding the mechanism of opioid drug action, particularly as it relates to cellular and differentiated tissue opiate receptors.

Opioid drugs typically are classified by their binding selectivity in respect of the cellular and differentiated tissue receptors to which a specific drug species binds as a ligand. These receptors include mu (μ), delta (δ), sigma (σ) and kappa (κ) receptors.

The well-known narcotic opiates, such as morphine and its analogs, are selective for the opiate mu receptor. Mu receptors mediate analgesia, respiratory depression, and inhibition of gastrointestinal transit. Kappa receptors mediate analgesia and sedation. Sigma receptors mediate various biological activities.

The existence of the opioid delta receptor is a relatively recent discovery which followed the isolation and characterization of endogenous enkephalin peptides which are ligands for the delta receptor. Research in the past decade has produced significant information about the delta receptor, but a clear picture of its function has not yet emerged. Delta receptors mediate

analgesia, but do not appear to inhibit intestinal transit in the manner characteristic of mu receptorstransit in the manner characteristic of mu

Opioid agents frequently are characterized as either agonists or antagonists. Agonists and antagonists are agents which recognize and bind to receptors, affecting (either initiating or blocking) biochemical/physiological sequences, a process known as transduction. Agonists inhibit or suppress neurotransmitter outputs in tissues containing receptors, e.g., inhibiting pain responses, or affecting other output-related phenomena. Antagonists also bind to receptors, but do not inhibit neurotransmitter outputs. Thus, antagonists bind to the receptor sites and block the binding of agonist species which are selective for the same receptor.

Concerning specific receptor ligands, the distinction between delta receptor agonists and antagonists heretofore has been made by their activity in the electrically stimulated mouse vas deferens assay, which typically has been considered the appropriate diagnostic tissue for the delta receptor. By contrast, mu receptor agonists are generally characterized by their activity in the electrically stimulated guinea pig ileum assay.

Only a relatively small number of essentially pure delta receptor-selective agents is known. With the exception of the delta opioid receptor antagonists or agonists disclosed in U.S. Patent 4,816,586 and International Patent Application W093/15062, all known delta receptor-selective opioid compounds are peptides, including endogenous enkephalins and other endorphins, as well as exogenous peptide analogs. The previously synthesized exogenous peptide analogs have various associated disadvantages in terms of their stability, their potentially suitable delivery routes as administered drug agents, and their *in vivo* tissue distribution.

Various physiological effects of the known peptide-based opioid ligands have been studied, including: analgesia; respiratory depression; gastrointestinal effects; mental, emotional, and cognitive process function; and mediation/modulation of other physiological processes.

U.S. Patent 4,518,711 describes cyclic, conformationally constrained analogs of enkephalins. These compounds include both agonists and antagonists for the delta receptor.

In addition to the above-described references relating to opioid compounds, the art relevant to the compounds of the present invention includes the polyaryl piperazine compounds described in the various references identified below.

S. Goenechea, *et al.*, in "Investigation of the Biotransformation of Meclozine in the Human Body," *J. Clin. Chem. Clin. Biochem.*, 1988, 26(2), 105-15, describe the oral administration of a polyaryl piperazine compound in a study of meclozine metabolization in human subjects.

In "Plasma Levels, Biotransformation and Excretion of Oxatomide in Rats, Dogs, and Man," Meuldermans, W., *et al.*, *Xenobiotica*, 1984, 15(6), 445-62, there is disclosed a metabolic study of plasma levels, biotransformation, and excretion of oxatomide.

T. Iwamoto, *et al.*, in "Effects of KB-2796, A New Calcium Antagonist, and Other Diphenylpiperazines on [^{3}H]nitrendipine Binding," *Jpn. J. Pharmacol.*, 1988, 48(2), 241-7, describes the effect of a polyaryl piperazine of specified formula, as a calcium antagonist.

K. Natsuka, *et al.*, in "Synthesis and Structure-Activity Relationships of 1-Substituted 4-(1,2-Diphenylethyl)piperazine Derivatives Having Narcotic Agonist and Antagonist Activity," *J. Med. Chem.*, 1987, 30 (10), 1779-1787, disclose racemates and enantiomers of 1-substituted 4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine derivatives.

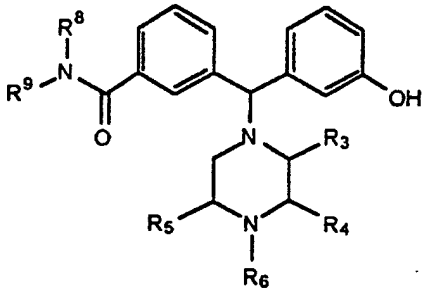
European Patent Application No. 458,160 describes substituted diphenylmethane derivatives which are said to be useful as analgesic and antiinflammatory agents, including compounds wherein the methylene bridging group (linking the two phenyl moieties) may have as a substituent on the methylene carbon a piperidinyl or piperazinyl group.

South African Patent Application No. 8604522 discloses N-substituted arylalkyl and aryl-alkylene substituted amino-heterocyclic compounds, including piperidine derivatives, which are described as useful cardiovascular, antihistamine, and anti-secretory agents.

European Patent Application No. 133,323 discloses certain diphenylmethyl piperazine compounds useful as non-sedative antihistamines.

There is a continuing need in the art for improved opioid compounds, particularly compounds which are free of adverse side effects of conventional opiates such as morphine and pethidine.

In particular, the present invention relates to diarylmethyl piperazine compounds of the formula:



(I)

wherein:

one of R^8 and R^9 is phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_3 alkoxy, C_1-C_3 alkyl and trifluoromethyl, and the other of R^8 and R^9 is hydrogen or saturated C_1-C_6 hydrocarbyl or unsaturated C_3-C_6 hydrocarbyl;
one of R^3 and R^5 is methyl and the other and R^4 are both hydrogen or one is hydrogen and the other is methyl; and R^6 is hydrogen, saturated C_1-C_6 hydrocarbyl, unsaturated C_3-C_6 hydrocarbyl or C_2-C_6 methoxyalkyl; or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

As used herein, in reference to the present invention, the term "alkyl" is intended to be broadly construed as encompassing alkyl groups of straight-chain as well as branched chain character.

As used herein, in reference to the present invention, the term "hydrocarbyl" is intended to encompass a group containing only carbon and hydrogen atoms which may contain double or triple bonds and which may be cyclic or aromatic in nature.

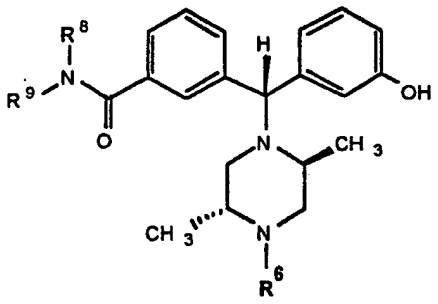
By "physiologically functional derivative" is meant a pharmaceutically acceptable salt, ester, ether or salt of an ester or ether of the compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) the said compound of formula (I) or an active metabolite or residue thereof. Phenolic C_1-C_6 alkyl ethers are a sub-class of physiologically functional derivatives of the compounds of formula (I).

In enantiomeric forms, compounds of the invention include individual enantiomers of the compounds of formula (I) in single species form substantially free of the corresponding enantiomer, as well as in admixture (in mixtures of enantiomeric pairs and/or in mixtures of multiple enantiomer species).

A sub-class of compounds within the scope of formula (I) are compounds wherein the hydrocarbyl group R^6, R^8 or R^9 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl.

A sub-class of compounds within the scope of formula (I) are compounds wherein R^3 and R^5 are both methyl and R^4 is hydrogen.

One preferred sub-class of compounds within the scope of the present invention comprises compounds of the formula:



(II)

wherein R^6 and R^8 and R^9 are as defined herein.

A further sub-class of compounds within the scope of formula (I) are compounds wherein R^6 is unsaturated C_3-C_6 hydrocarbyl, and preferably is allyl.

A further sub-class of compounds within the scope of formula (I) are compounds wherein one of R^8 and R^9 is phenyl optionally substituted with one substituent selected from halogen, C_1-C_3 alkoxy and trifluoromethyl.

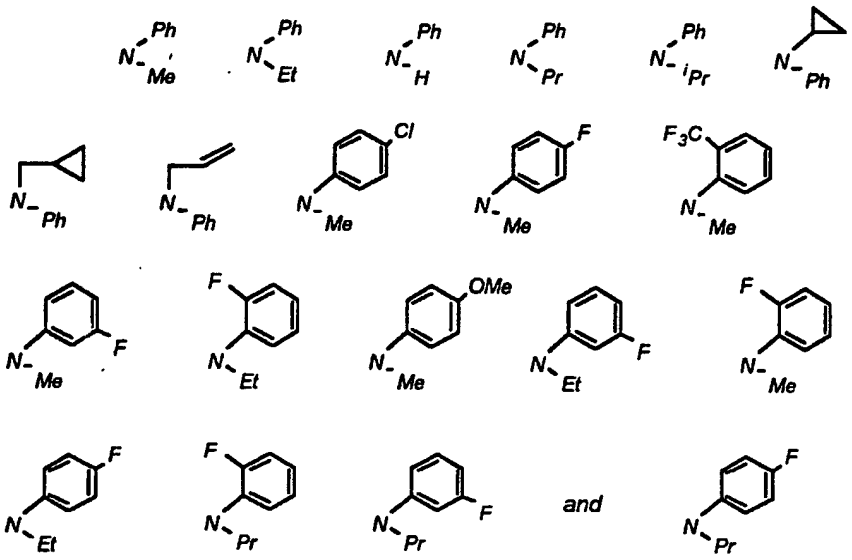
Preferably, halogen is chloro or fluoro and/or C_1-C_6 is methoxy.

A further sub-class of compounds within the scope of formula (I) are compounds wherein one of R^8 and R^9 is unsubstituted phenyl.

A further sub-class of compounds within the scope of formula (I) are compounds wherein

the other of R^8 and R^9 is hydrogen, saturated C_1-C_6 hydrocarbyl or allyl. Prerably, saturated C_1-C_6 hydrocarbyl is C_1-C_6 alkyl, such as methyl, ethyl or propyl (including n-, iso- and cyclo-propyl) or C_3-C_6 cycloalkyl.

In a specific and preferred aspect of diarylmethyl piperazine compounds of the above formula, NR^8R^9 may, for example, be selected from the group consisting of:



Illustrative compounds of the invention within the scope of the above general formula (I) include the benzamide compounds identified below.

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-fluorophenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-phenylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-chlorophenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-phenylbenzamide

(-)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-phenylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-methyl-N-(2-(trifluoromethyl)phenyl)benzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-(2,4,6-trichlorophenyl)benzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-phenyl-N-propylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-N-(4-methoxyphenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-allyl-N-phenylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(cyclopropyl)methyl-N-phenylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-isopropyl-N-phenylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-cyclopropyl-N-phenylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-propylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(3-fluorophenyl)benzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-propylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(2-fluorophenyl)benzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-methoxyphenyl)-N-propylbenzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-methoxyphenyl)benzamide;

(+)-3-((αS)-α-((2S, 5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-methyl-N-phenylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-methoxyphenyl)-N-propylbenzamide;

3-((αR)-α((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(N-(3-fluorophenyl)-N-methylcarbamoyl) benzyl)phenyl monophosphate

and pharmaceutically acceptable ethers, esters or salts thereof or physiologically functional derivatives thereof.

Particular preferred compounds from the above-listed illustrative compounds of the invention include

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-fluorophenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-phenylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-phenylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-phenyl-N-propylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-N-(4-methoxyphenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-methylbenzamide

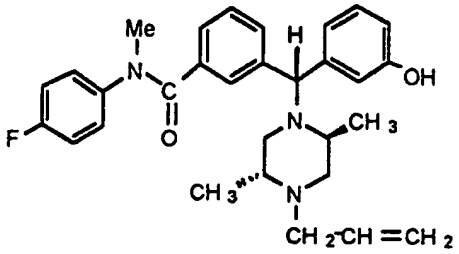
(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide

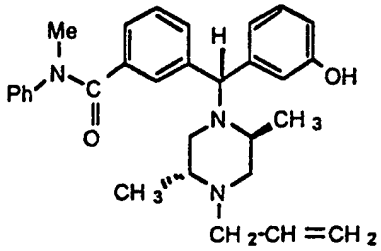
and pharmaceutically acceptable ethers, esters or salts thereof or phsiologically functional derivatives thereof.

Table I below shows the chemical structure of the eight above-identified particularly preferred compounds of the present invention, denoted herein as compounds "A", "B", "C", "D", "E", "F", "G" and "H", respectively.

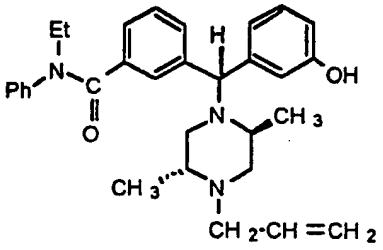
Table I



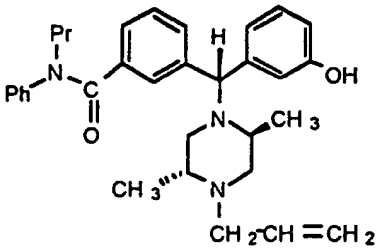
"A"



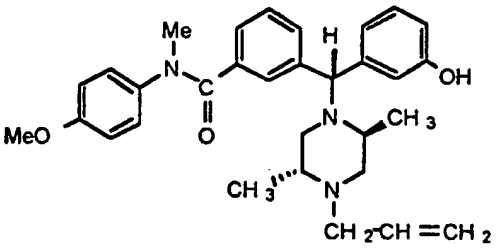
"B"



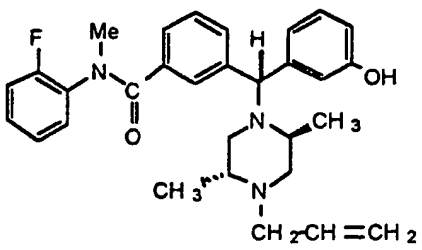
"C"



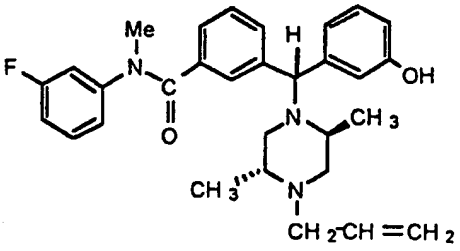
"D"



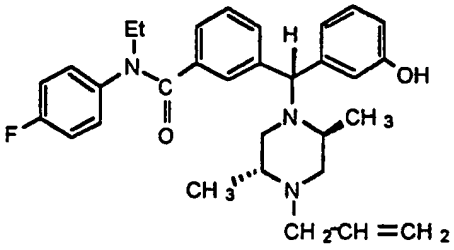
"E"



"F"



"G"



"H"

Compounds of the above general formula (I) exhibit binding selectivity for receptor(s). Depending on the structure and stereo-specificity of the particular formula (I) compounds, such compounds may exhibit binding ability to receptor(s) selected from the group consisting of delta receptors, mu receptors, kappa receptors, sigma receptors, and combinations of such receptors.

Various compounds within general formula (I) exhibit delta receptor agonist activity including mediating analgesia. Other compounds of such general formula exhibit delta receptor antagonist activity, as hereinafter more fully described. Still other compounds within the general formula exhibit mu receptor activity, and more particularly, in some instances, mixed mu receptor/delta receptor activity.

Examples of pharmaceutically acceptable esters of the invention include carboxylic acid esters of hydroxy groups in compounds of formula (I) in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (e.g. n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g. methoxymethyl), arylalkyl (e.g. benzyl), aryloxyalky (e.g. phenoxymethyl), and aryl (e.g. phenyl); alkyl- or arylalkylsulfonyl (e.g. methanesulfonyl); amino acid esters (e.g. L-valyl or L-isoleucyl); dicarboxylic acid esters (e.g. hemisuccinate); carbonate esters (e.g. ethoxycarbonyl); carbamate esters (e.g. dimethylaminocarbonyl, (2-aminoethyl)aminocarbonyl); and inorganic esters (e.g. mono-, di- or triphosphate).

Examples of pharmaceutically acceptable salts of the compounds of formula (I) and physiologically functional derivatives thereof include salts derived from an appropriate base, such as an alkali metal (for example, sodium, potassium), an alkaline earth metal (for example, calcium, magnesium), ammonium and NX_4^+ (wherein X is C_{1-4} alkyl). Pharmaceutically acceptable salts of an amino group include salts of: organic carboxylic acids such as acetic, lactic, tartaric, malic, lactobionic, fumaric, and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, isethionic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric and sulfamic acids. Pharmaceutically acceptable salts of a compound having a hydroxy group consist of the anion of said compound in combination with a suitable cation such as Na^+, NH_4^+, or NX_4^+ (wherein X is for example a C_{1-4} alkyl group).

As used herein, in reference to the present invention, the term "aryl" is intended to be broadly construed as referring to carbocyclic as well as heterocyclic aromatic groups.

For therapeutic use, salts of compounds of formula (I) will be pharmaceutically acceptable, i.e., they will be salts derived from a pharmaceutically acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether or not derived from a pharmaceutically acceptable acid or base, are within the scope of the present invention.

Compounds of the present invention have utility as exogenous receptor combinant compounds, i.e., compounds useful for binding with a receptor, such as delta receptor, mu receptor, sigma receptor, kappa receptor, or two or more of such receptors. The combinant compound may be a conjugate in an agonist/antagonist pair which may be employed for transductional assay of neurotransmitter function in appertaining cellular or differentiated tissue systems. In addition to receptor assay, differential binding, and specificity applications for cellular, histological, and corporeal monitoring and assessment purposes, the compounds of the present invention exhibit specific bioactivity characteristics rendering them useful as treatment agents for various physiological and pathological conditions.

The compounds of the present invention include agonist species useful for the treatment of pain, diarrhea, depression, urinary incontinence, mental illness, cough, lung edema, gastrointestinal disorders, spinal injury, and drug addiction.

The compounds of the present invention also include antagonist species which as mentioned are useful as agonist conjugates for neurotransmitter assay applications as well as antagonist species with utility for treatment of alcohol abuse, and drug overdose of opiate or other agonist species.

In addition, to the extent that degeneration or dysfunction of opioid receptors is present or implicated in a disease state involving tissue or discrete cellular loci, isotopically labeled versions of opioid compounds of the present invention find utility in diagnostic and imaging applications, e.g., diagnostic techniques involving positron emission tomography (PET) scans of the brain.

As mentioned hereinabove, opioid receptor sites are loci on cells which recognize and bind opiate and opioid drugs, which in turn can affect (initiate/block) biochemical/physiological sequences (transduction).

In the case of the non-peptide opioid agents contemplated by the present invention, the structure/activity pattern for the various compounds within the general formula (I) is highly diverse, and subtle differences such as changes in stereochemistry can result in different transductional effects. Thus, formula (I) comprehends agonist species as well as antagonist species.

In the case of delta receptor agonists, activity is generally distinguished and measured by activity in the electrically stimulated mouse vas deferens assay.

Further, empirical determinations utilizing compounds of the present invention provide strong evidence of the existence of a delta receptor subtype in the brain that is different from the delta receptor in the mouse vas deferens.

In consequence of the existence of such delta receptor subtypes, other receptor binding assays or screening techniques, e.g., analgesia screening tests, may be employed as a further predictor of agonist or antagonist activity for specific compounds of the present invention.

In the case of mu receptor agonists, activity is generally distinguished and measured by activity in the electrically stimulated guinea pig ileum assay.

The compounds A, B, C, D, E, F, G and H are highly selective opioid receptor ligand species. All are efficacious in mediating analgesia. In general, the spectrum of analgesic utilities of diarylmethyl piperazine compounds of the invention may be readily determined without undue experimentation by simple receptor binding screening tests. In this respect, and merely by way of

illustration, the diarylmethyl piperazine compounds of the invention which are predominantly mu receptor agonists may be utilized for example in mediating surgical analgesia. Diarylmethyl piperazine compounds of the invention which are predominantly delta receptor agonists may be utilized for example in mediating epidural analgesia. Diarylmethyl piperazine compounds of the invention which are mixed mu/delta opioid agonists, e.g., Compounds A, B, C, D, E, F, G and H, may be utilized for example in mediating surgical and/or post-operative analgesia.

The mixed mu/delta receptor character of various compounds within the scope of the present invention entails a substantial advantage over various known mu receptor compounds currently employed as analgesics.

The vast majority of currently used high potency analgesics, including morphine, fentanyl, meperidine, sufentanil, and codeine, are mu receptor binding compounds. As is well established, these compounds, while highly efficacious for mediating analgesia, have accompanying side effects, including disorientation, attenuation of mental acuity, muscle rigidity, and respiratory depression, and withdrawal side-effects including nausea, vomiting, shakes, seizures, and sweats. Such side effects are typically absent or at least much reduced in use of analgesia-mediating delta receptor binding species. Accordingly, the use of mixed mu/delta receptor species of the present invention may attenuate or even eliminate the side effects normally attendant the use of mu receptor binding compounds.

The compounds of the invention when used in pharmaceutical or diagnostic applications desirably are prepared in substantially pure enantiomer form, with an enantiopurity of at least 90% enantiomeric excess (EE), preferably at least 95% EE, more preferably at least 98% EE, and most preferably at least 99% EE. Enantiomeric excess values provide a quantitative measure of the excess of the percentage amount of a major isomer over the percentage amount of a minor isomer which is present therewith, and may be readily determined by suitable methods well-known and established in the art, as for example chiral high pressure liquid chromatography (HPLC), chiral gas chromatography (GC), nuclear magnetic resonance (NMR) using chiral shift reagents, etc.

Compounds A, B, C, D, E, F, G and H are enantiomerically pure analgesic agents exhibiting agonism at both mu and delta opioid receptors. In rodent test subjects, for example,

these compounds produce analgesia comparable to mu-analgesic morphine, but produce a much reduced extent of muscle rigidity and respiratory depression. Further, rodent tests show these compounds to be free of proconvulsant activity, such as may be associated with structurally related pure delta agonists.

Although it might be assumed at first impression that all delta agonist compounds of the present invention would have similar *in vivo* profiles, with potencies parallel to mouse vas deferens activity, this is not invariably the case.

The diarylmethyl piperazine compounds of the invention include compounds which have significant potency in the receptor binding assay (rat brain), compounds that are predominantly active at one or the other of the delta receptor subtypes, and compounds having mu receptor activity or mixed mu receptor/delta receptor activity.

Binding assay and analgesia test results show that compounds of the present invention variously mediate analgesia in respect of a wide variety of stimuli and physiological perturbations. This in turn evidences a high level of complexity in neurotransmitter functions and stimulus-related responses associated with various opioid receptors, including mu receptors, delta receptors and delta receptor sub-types.

A number of compounds of the present invention within formula (I), or their chemical precursors (which also in many instances constitute novel compounds and thus are contemplated within the scope of the present invention), evidence biological activities in addition to opioid activity, e.g., biological activity including sigma receptor binding affinity, and multidrug resistance activity.

As is apparent from the foregoing discussion, the compounds of the present invention have broad utility in the treatment of a wide variety of physiological conditions and disorders. The invention accordingly contemplates the use of such compounds in the manufacture of a medicament for the treatment or prophylaxis of such physiological conditions and disorders. In addition to those treatment applications already mentioned, other utilities for compounds of the

present invention include the treatment of bronchial disorders such as asthma, emphysema, and apnea.

Further, endogenous opioids such as enkephalins and endorphins, and their neurological systems, have been identified in connection with various CNS disorders, such as compulsive behavior, depression, psychosis, etc., and agonist or antagonist species within formula (I) of the present invention have utility in combatting such disorders.

Various agonist species as well as antagonist species of the compounds of formula (I) also find utility in the treatment of drug (opioid/narcotic) abuse/addiction, and thus have utility for replacement of methadone or other conventional opiate agents in drug rehabilitation programs, to the extent that conventional drug treatment agents have side effects or other disadvantages which contraindicate or limit their use.

Concerning drug addiction treatment with effective compounds within the broad scope of the present invention, it is noted that methadone is a mu-receptor opiate with actions similar to morphine, i.e., methadone is abusable and addictive. Methadone is used as a "maintenance therapy" agent for opiate addicts, so that such individuals can remain functional while satisfying their addictions in a safer and non-criminal manner. In this respect, compounds of the invention may have utility in place of, or as an adjunct to, currently used treatments for drug addiction, such as those involving naltrexone, methadone, clonidine, etc.

Certain compounds within the scope of the present invention, as discussed above, have utility in effecting local analgesia, such as spinal analgesia, and compounds of the invention may also find utility in appetite suppression applications, and the like.

Compounds of the present invention include various compounds which are delta-opioid agonists in the mouse vas deferens delta receptor subtype, as well as compounds which are antagonists at such delta receptor subtype. The compounds of the present invention also include compounds which are agonists or antagonists at the delta receptor in the brain, which appears, on the basis of empirical determinations, to be a different delta receptor subtype than the delta receptor in the mouse vas deferens. A substantial number of compounds of the aforementioned

general formula (I) of the invention have either agonist or antagonist activity at both delta receptor subtypes. A number of these compounds have high activity at the mu-opioid receptor, either as pure mu receptor binding compounds or as mixed mu receptor/delta receptor binding compounds, and still other compounds within the broad scope of the present invention have significant affinity for the sigma receptor.

In *in vitro* tests for agonist/antagonist activity, such as receptor binding affinity tests, and inhibition of electrically stimulated muscle twitch tests, compounds of the present invention exhibit potency over a range of from nanomolar to micromolar concentrations, depending on the specific compound employed.

Compounds of the present invention have pharmaceutical activity, including, *inter alia*, analgesic activity, and are useful in treating animals, e.g., mammals such as humans, for conditions in which analgesia is desired.

A method of producing an analgesic response in an animal subject in need of such treatment comprises administering to the animal subject an analgesia-inducing amount of a compound of formula (I).

In addition, various compounds of the present invention having appertaining therapeutic utility may be usefully employed in the treatment of conditions including: drug and alcohol addiction/overdose; mental, emotional, and cognitive disorders; cough; lung edema; and gastrointestinal disorders. Correspondingly, the present invention contemplates a method of treating an animal subject having such condition(s) and in need of such treatment, comprising administering to such animal an effective amount of a compound of the present invention which is therapeutically effective for said condition.

Subjects to be treated by the methods of the present invention include both human and non-human animal (e.g., bird, dog, cat, cow, horse) subjects, and are preferably mammalian subjects, and most preferably human subjects.

Depending on the specific condition to be treated, animal subjects may be administered compounds of formula (I) at any suitable therapeutically effective and safe dosage, as may readily be determined within the skill of the art, and without undue experimentation.

In general, while the effective dosage of compounds of the invention for therapeutic use may be widely varied in the broad practice of the invention, depending on the specific application, condition, or disease state involved, as readily determinable within the skill of the art, suitable therapeutic doses of the formula (I) compounds, for each of the appertaining compositions described herein, and for achievement of therapeutic benefit in treatment of each of the conditions described herein, will be in the range of 1 microgram (μg) to 100 milligrams (mg) per kilogram body weight of the recipient per day, preferably in the range of 5 μg to 75 mg per kilogram body weight per day, and most preferably in the range of 10 μg to 50 mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five, six, or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing from 10 μg to 1000 mg, preferably from 50 μg to 500 mg, more preferably from 50 μg to 250 mg, and most preferably from 50 μg to 10 mg of active ingredient per unit dosage form. Alternatively, if the condition of the recipient so requires, the doses may be administered as a continuous infusion.

The mode of administration and dosage forms will of course affect the therapeutic amounts of the compounds which are desirable and efficacious for the given treatment application.

For example, orally administered dosages typically are at least twice, e.g., 2-10 times, the dosage levels used in parenteral administration methods, for the same active ingredient. In oral administration for inducing analgesia, dosage levels for mu receptor binding compounds of the invention may be on the order of 5-200 mg/70 kg body weight/day. Intrathecal administration dosage levels generally are on the order of about 10% of the levels characteristic of parenteral administration dosage levels. In tablet dosage forms, typical active agent dose levels suitable for inducing analgesia are on the order of 10-100 mg per tablet.

The compounds of formula (I) may be administered per se as well as in the form of pharmaceutically acceptable esters, ethers, salts, and other physiologically functional derivatives thereof.

The present invention also contemplates pharmaceutical formulations, both for veterinary and for human medical use, which comprise as the active agent one or more compound(s) of the invention, and a pharmaceutically acceptable carrier. The invention also provides the use of a compound of the invention, such as a compound within the above-discussed formulae (I) and (II), in the manufacture of a medicament for the treatment or prophylaxis of the conditions and disorders variously described herein.

In such pharmaceutical and medicament formulations, the active agent preferably is utilized together with one or more pharmaceutically acceptable carrier(s) therefor and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not unduly deleterious to the recipient thereof. The active agent is provided in an amount effective to achieve the desired pharmacological effect, as described above, and in a quantity appropriate to achieve the desired daily dose.

The formulations include those suitable for parenteral as well as non-parenteral administration, and specific administration modalities include oral, rectal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, intrathecal, intra-articular, intra-arterial, sub-arachnoid, bronchial, lymphatic, and intra-uterine administration. Formulations suitable for parenteral administration are preferred.

When the active agent is utilized in a formulation comprising a liquid solution, the formulation advantageously may be administered parenterally. When the active agent is employed in a liquid suspension formulation or as a powder in a biocompatible carrier formulation, the formulation may be advantageously administered orally, rectally, or bronchially.

When the active agent is utilized directly in the form of a powdered solid, the active agent may advantageously administered orally. Alternatively, it may be administered bronchially, via

nebulization of the powder in a carrier gas, tc form a gaseous dispersion of the powder which is inspired by the patient from a breathing circuit comprising a suitable nebulizer device.

In some applications, it may be advantageous to utilize the active agent in a "vectorized" form, such as by encapsulation of the active agent in a liposome or other encapsulant medium, or by fixation of the active agent, e.g., by covalent bonding, chelation, or associative coordination, on a suitable biomolecule, such as those selected from proteins, lipoproteins, glycoproteins, and polysaccharides.

The formulations comprising the active agent of the present invention may conveniently be presented in unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods generally include the step of bringing the active compound(s) into association with a carrier which constitutes one or more accessory ingredients. Typically, the formulations are prepared by uniformly and intimately bringing the active compound(s) into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into dosage forms of the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient as a powder or granules; or a suspension in an aqueous liquor or a non-aqueous liquid, such as a syrup, an elixir, an emulsion, or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which optionally is mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent, or discharging agent. Molded tablets comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

A syrup may be made by adding the active compound to a concentrated aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include flavorings, suitable preservative, agents to retard

crystallization of the sugar, and agents to increase the solubility of any other ingredient, such as a polyhydroxy alcohol, for example glycerol or sorbitol.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound, which preferably is isotonic with the blood of the recipient (e.g., physiological saline solution). Such formulations may include suspending agents and thickening agents and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose form.

Nasal spray formulations comprise purified aqueous solutions of the active compounds with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes.

Formulations for rectal administration may be presented as a suppository with a suitable carrier such as cocoa butter, hydrogenated fats, or hydrogenated fatty carboxylic acids.

Ophthalmic formulations are prepared by a similar method to the nasal spray, except that the pH and isotonic factors are preferably adjusted to match that of the eye.

Topical formulations comprise the active compound dissolved or suspended in one or more media, such as mineral oil, petroleum, polyhydroxy alcohols, or other bases used for topical pharmaceutical formulations.

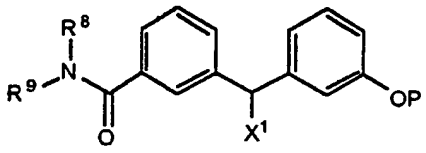
Transdermal formulations may be prepared by incorporating the active agent in a thixotropic or gelatinous carrier such as a cellulosic medium, e.g., methyl cellulose or hydroxyethyl cellulose, with the resulting formulation then being packed in a transdermal device adapted to be secured in dermal contact with the skin of a wearer.

In addition to the aforementioned ingredients, formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents,

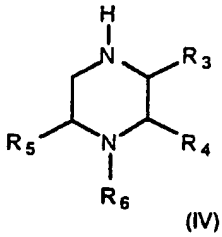
binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants), and the like.

The present invention also contemplates a process for the preparation of a compound of formula (I), as defined hereinabove, or a pharmaceutically acceptable ester, ether, salt, or other physiologically functional derivative thereof, said process comprising a synthesis procedure selected from the group consisting of synthesis procedures (A), (B) and (C) below:

(A) the alkylation of a piperazine of formula (IV) by an alkylating agent of formula (III),



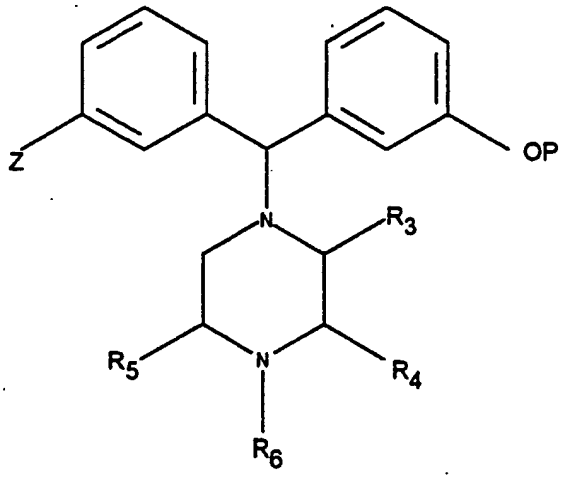
(III)



(IV)

wherein R^3 to R^6 and R^8 and R^9 are as defined in any of the preceding claims, P is hydrogen or an hydroxy-protecting group and X^1 is a leaving group; and, when R^6 is hydrogen, optionally alkylating the resulting compound of formula (I) with an alkylating agent of the formula R^6-X^1, wherein R^6 is saturated C_1-C_6 hydrocarbyl, unsaturated C_3-C_6 hydrocarbyl or C_2-C_6 methoxyalkyl and X^1 is a leaving group, or optionally alkylating the resulting compound of formula (I) by reductive amination with a C_1-C_6 aldehyde in the presence of a reducing agent;

(B) reacting a compound of formula (V),



(V)

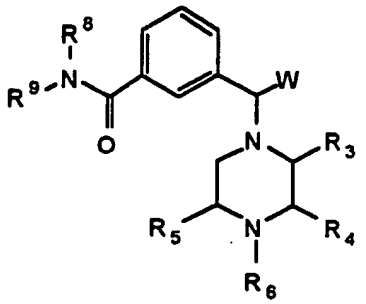
wherein R^3 to R^6 are as defined above, P is as defined above and Z is bromo, iodo or trifluoromethylsulphonyl as appropriate, with

(a) in the case where Z is bromo or iodo; an alkyl metal, or suitably reactive metal, optionally transmetallating the resulting metallic compound with a transition metal species to provide a different metallic compound, reacting the resulting metallic compound with carbon dioxide and converting the resulting carboxylic acid to the corresponding acid chloride, anhydride or ester, and reacting the resulting acid chloride, anhydride or ester with an amine of the formula HNR^8R^9 wherein R^8 and R^9 are as defined herein or reacting the resulting metallic compound with an aminocarbonyl chloride compound of formula $ClCONR^8R^9$, wherein R^8 and R^9 are as defined herein; or

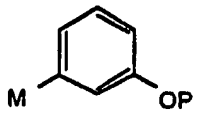
(b) in the case where Z is bromo, iodo or trifluoromethylsulphonyl; a cyanating reagent, hydrolyzing the resulting nitrile with alkali or aqueous mineral acid, converting the resulting carboxylic acid to the corresponding acid chloride, anhydride or ester, and reacting the resulting acid chloride, anhydride or ester with an amine of the formula HNR^8R^9 wherein R^8 and R^9 are as defined herein; or

(c) in the case where Z is bromo, iodo or trifluoromethylsulphonyl; excess amine of the formula HNR^8R^9 wherein R^8 and R^9 are as defined herein and carbon monoxide in the presence of a transition metal catalyst to yield a compound of formula (I), wherein R^8 and R^9 are as defined herein; or

(C) reacting a compound of formula (VI), with a phenylmetallic compound of formula (VII):



(VI)



(VII)

wherein R^3 to R^6 and R^8 and R^9 are as defined herein, P is hydrogen or a hydroxy-protecting group, M is a metal species and W is benzotriazolyl or trichlorotitaniumoxy; (Katritzky, A.R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L; J.Chem. Soc., Perkin Trans. 1, 1139, (1989); Seebach, D.; Betscart, C.; Schiess, M. Helv. Chim. Acta, 67, 1593. (1984)) and, when P is an hydroxy-protecting group, deprotecting the hydroxy group;

optionally converting the resulting compound of formula (I) into a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

Procedure A

The reaction between an alkylating agent of formula (III) and a piperazine of formula (IV) may be carried out in a solvent such as toluene or acetonitrile.

Alkylating agents of the formula R^6-X^1 are commercially available or may be prepared by published procedures. As an alternative to alkylation with an alkylating agent R^6-X^1, the method of reductive amination may be employed in which an appropriate commercially available C^1-C^6 aldehyde is reduced with a reducing agent such as sodium cyanoborohydride in solvents such as alcohols or ethers.

Procedure B

(a) A compound of formula (I) may be prepared from a compound of formula (V), wherein Z is bromo or iodo and P is a hydroxy-protecting group, such as tert-butyldimethylsilyl, by low-temperature (e.g. -60 °C to -78 °C) metal exchange of the reactive halogen with an organometallic reagent, such as n-butyllithium, or an activated form of a metal, such as lithium or magnesium, to provide an intermediate metallic compound, followed by reaction with carbon dioxide to provide the carboxylic acid in an anhydrous solvent such as tetrahydrofuran, under an inert atmosphere (e.g. nitrogen). The carboxylic acid may then be converted to the carboxamide of formula (I) by the methods described below.

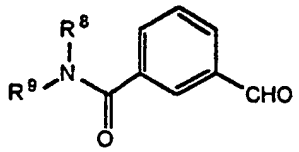
Alternatively, the intermediate metallic compound generated from a compound of formula (V) may be treated with an appropriate carbamoyl chloride ($ClCONR^8R^9$) to produce a compound of formula (I).

(b) A compound of formula (I) may also be prepared from a compound of formula (V) wherein Z is bromo, iodo or triflate (trifluoromethylsulphonyl) by treatment with a cyanating reagent, such as cuprous cyanide, in a suitable solvent such as dimethylformamide or N-methylpyrrolidinone, to provide the corresponding compound of formula (V) wherein Z is nitrile, which may be further hydrolyzed to the corresponding carboxylic acid with alkali or aqueous mineral acid. The carboxylic acid may then be converted to a compound of formula (I) by various means known in the art, such as formation of the acid chloride (e.g. with thionyl chloride or oxalyl chloride) or by formation of the mixed anhydride (e.g. with isobutyl chloroformate) or by formation of an activated ester with conventional peptide-coupling reagents (e.g. dicyclohexylcarbodiimide or benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate), any of which activated intermediates may be converted to the desired carboxamide of formula (I) by reaction with an appropriate amine (HNR^8R^9) in a suitable solvent such as dichloromethane or dimethylformamide.

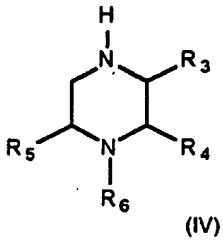
(c) A compound of formula (I) may also be prepared from a compound of formula (V), wherein Z is bromo, iodo or triflate, by treatment with a transition metal catalyst, such as tetrakis(triphenylphosphine)palladium, in the presence of excess amine and carbon monoxide in a solvent such a tetrahydrofuran or acetonitrile.

Procedure C

A compound of formula (VI) may be prepared as a reactive intermediate by combining an aldehyde of formula (VIII) with a piperazine of formula (IV)



(VIII)

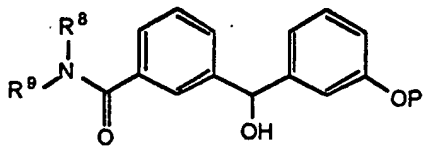


(IV)

wherein R^3 to R^6 and R^8 and R^9 are as defined herein, in the presence of titanium tetrachloride or benzotriazolyl in a suitable solvent such as toluene or dichloromethane, or for an intermediate of formula (VI) where W is benzotriazole, the reactive intermediate may be isolated, if desired, by crystallization or other appropriate means.

A compound of formula (I) may be obtained as a single enantiomeric species by classical resolution with an enantiopure acid, such as mandelic acid, or by formation of readily separable diastereomers by an enantiopure derivatizing agent, or by chiral chromatography, or by enzymatic resolution of a compound of formula (I) or a suitable derivative, or by preparation of the compound of formula (I) from enantiopure precursors, which may themselves be obtained as single enantiomers by similar means.

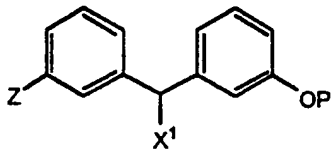
Compounds of formula (III) may be obtained from the appropriate alcohols of formula (IX), where the phenol is protected with a suitable protecting group P, by methods such as halogenation with thionyl chloride or triphenylphosphine/carbon tetrabromide, or reaction with methanesulfonyl chloride or toluenesulfonyl chloride, in a solvent such as dichloromethane.



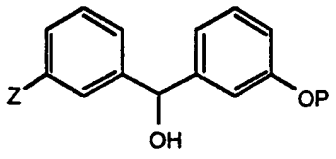
(IX)

Piperazines of formula (IV) are commercially available, or may be prepared by published procedures or variations of published procedures where R^6 is varied by appropriate alkylation with agents R^6-X^1.

Compounds of formula (V) may be prepared by alkylation of a piperazine of formula (IV) with an alkylating agent of formula (X), in similar fashion to the piperazine alkylation described above. Alkylating agents of formula (X) are likewise obtained from alcohols of formula (XI) by similar methods to those described above for compounds of formula (III).

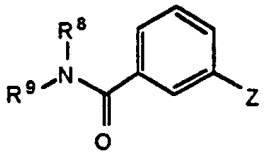


(X)

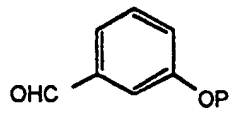


(XI)

Alcohols of formula (IX) or (XI) may be prepared by low-temperature (e.g. -60 °C to -78 °C) addition of substituted arylmetallic species, prepared from compounds of formula (XII), wherein Z is reactive halogen (e.g. iodine or bromine), by methods described hereinabove, to protected benzaldehydes of formula (XIII).

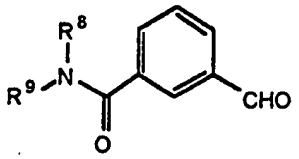


(XII)

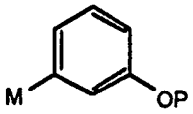


(XIII)

Conversely, compounds of formula (IX) or (XI) may also be formed by similar addition of aforementioned protected phenylmetallic species (VII) to benzaldehydes of formula (VIII).



(VIII)



(VII)

Compounds (VII), (VIII), (XII) and (XIII) and their suitably protected derivatives may be prepared from commercially available materials by standard literature procedures.

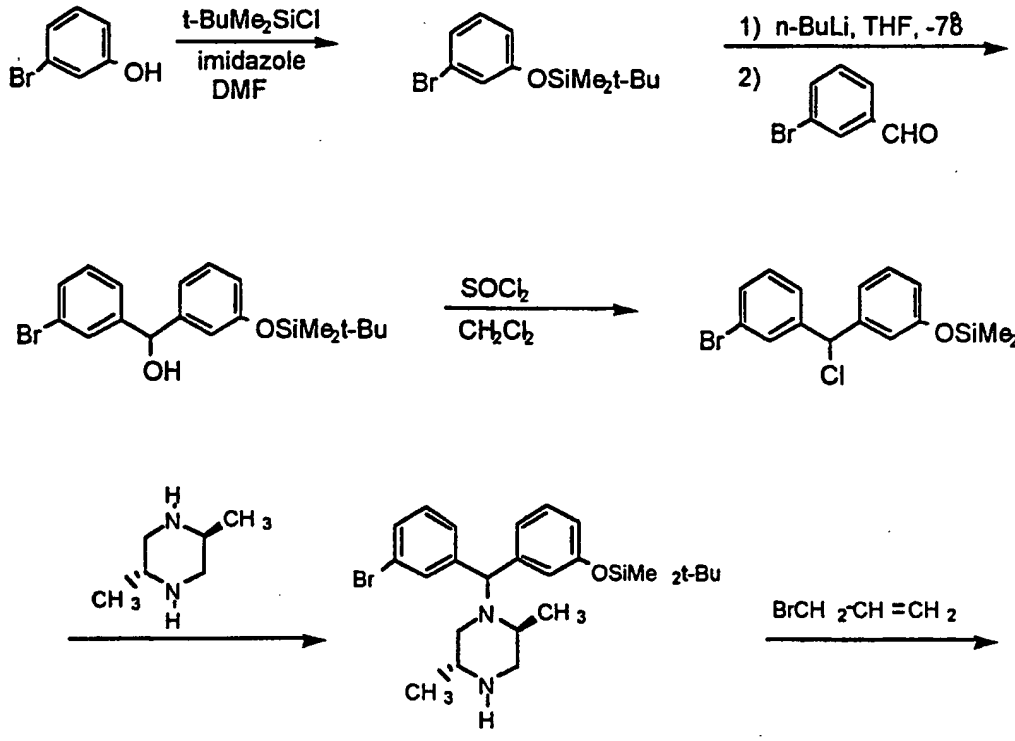
A compound of formula (I) may be converted into a pharmaceutically acceptable ester by reaction with an appropriate esterifying agent, e.g. an acid halide or anhydride. The compound of formula (I), including esters thereof, may be converted into pharmaceutically acceptable salts thereof in conventional manner, for example, by treatment with an appropriate acid. An ester or salt of a compound of formula (I) may be converted into the parent compound, for example, by hydrolysis. Phenolic ethers, of a compound of formula (I) wherein P is C_1-C_6 alkyl, may be prepared as described hereinbefore.

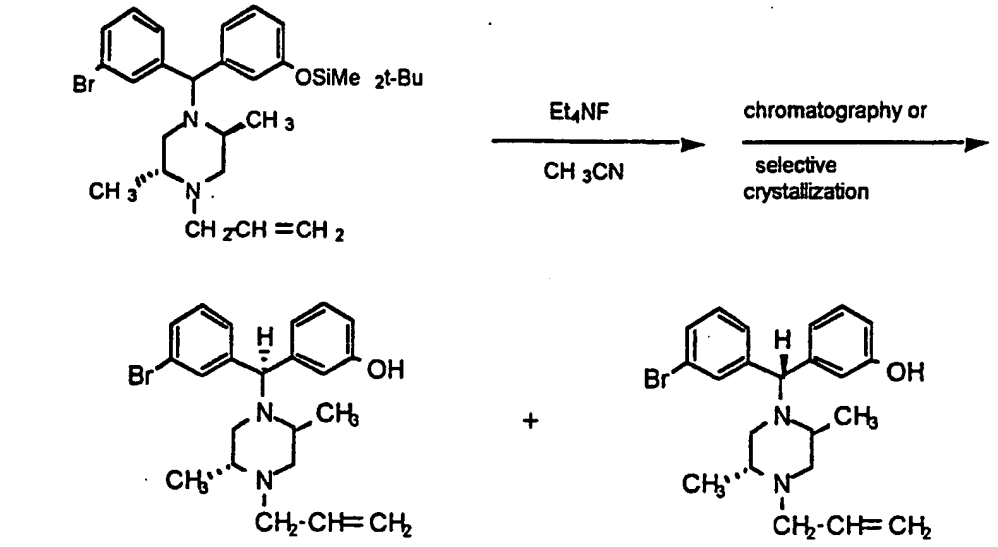
Based on the foregoing as well as general synthesis considerations, it will be appreciated that various syntheses are useful for preparation of diarylmethyl piperazine compounds of the present invention, as will be readily apparent to those of ordinary skill in the art. Illustrative synthetic methods for production of compounds within the broad scope of the present invention are set out below by way of example, it being understood that compounds of the invention are amenable to manufacture by various other synthesis routes and methods within the skill of the art, and that the illustrative synthesis methods set out below are therefore not to be limitingly construed as regards the scope of the invention. It is to be further appreciated that the novel compounds of the present invention comprehend various novel intermediates, precursors, pro-drugs, analogues, and derivatives of compounds specifically identified herein with reference to the invention.

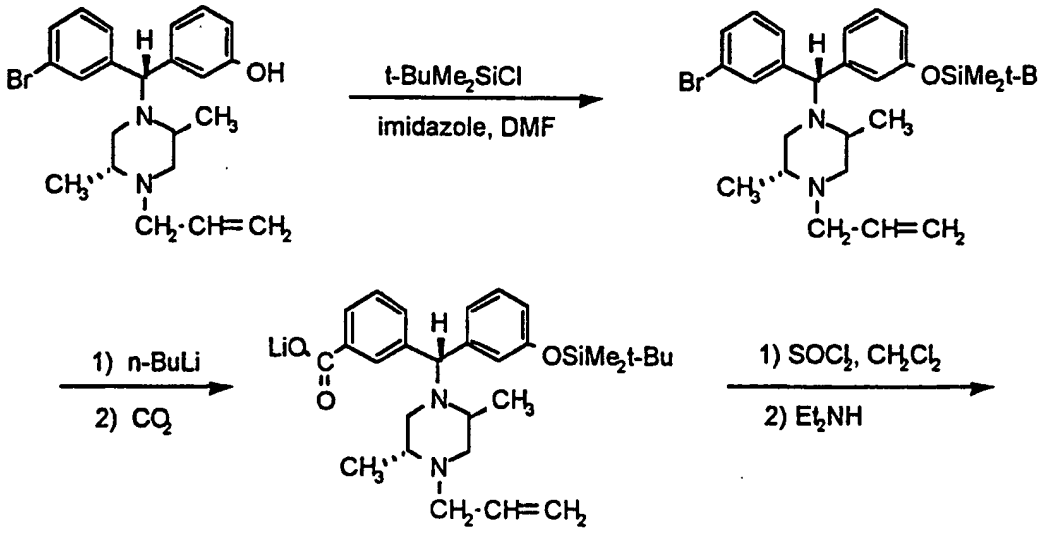
When the synthesis procedures which are employed for producing compounds of the invention yield racemic mixtures as reaction products, such racemic mixtures may be resolved by suitable means and methods well-known and established in the art, as for example by formation of

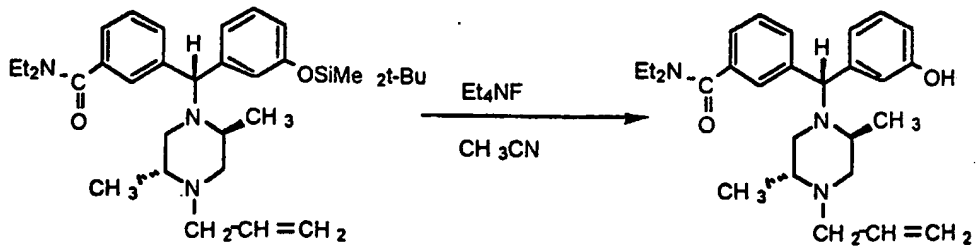
diastereomeric salts with enantiopure carboxylic acids, by chiral chromatographic resolution, by enzymatic resolution, or by other suitable conventional methods.

Set out below are illustrative synthetic schemes for the formation of racemic (±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide, hereafter referred to as Compound (±)-I, which may be obtained as its constituent enantiomers by applying classical resolution or chiral synthesis methods to the final product or to appropriate intermediates. Such methods are further illustrated for the obtention of the enantiomer (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide, referred to herein as Compound I, which is more specifically described in (Reference) Example 1 hereof. The illustrative synthesis schemes and resolution methodology of the ensuing description may likewise be employed in the synthesis and resolution of compounds of the invention, or alternatively other synthesis and/or resolution methodologies may be usefully employed within the skill of the art.



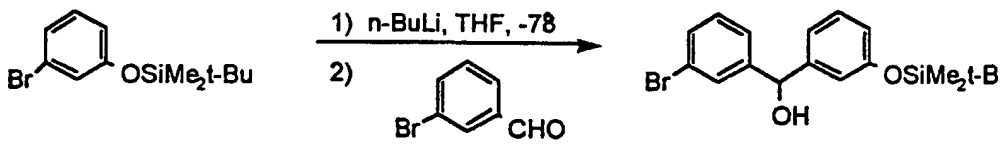

Br
OSiMe 2t-Bu
CH 3
CH 3
CH 2CH =CH 2
Et4NF
CH 3CN
chromatography or
selective
crystallization
Br
OH
CH3
CH3
CH2-CH= CH2
+
Br
OH
CH3
CH3
CH2-CH= CH2


Br
OH
CH3
CH3
CH2-CH= CH2
t-BuMe2SiCl
imidazole, DMF
Br
OSiMe2t-B
CH3
CH3
CH2-CH= CH2
1) n-BuLi
2) CO2
LiO
C
O
OSiMe2t-Bu
CH3
CH3
CH2-CH= CH2
1) SOCl2, CH2Cl2
2) Et2NH

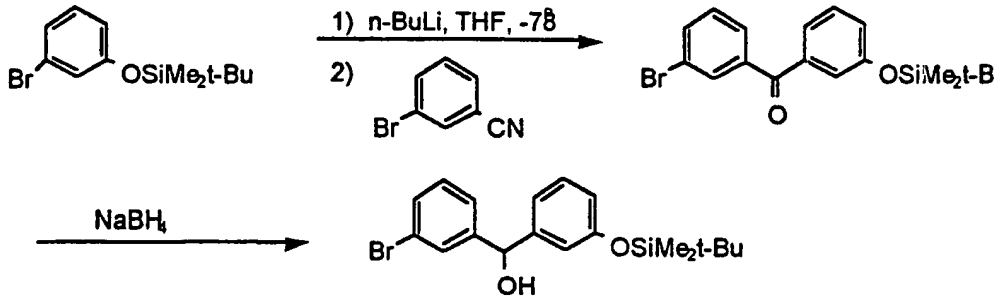


Compound (±)-I

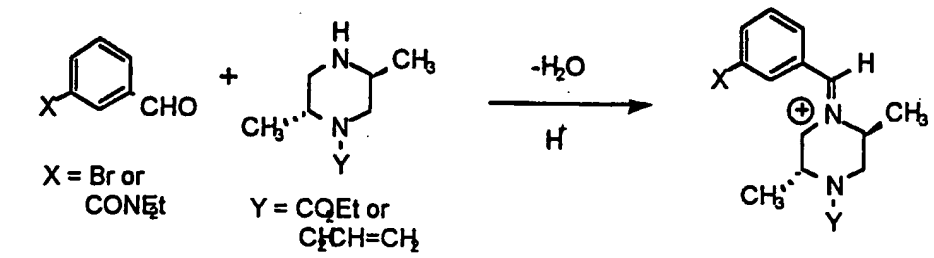
With respect to the foregoing synthesis scheme, the initial benzhydryl alcohol could be prepared from 3-(t-butyldimethylsilyloxy)bromobenzene by the following scheme:

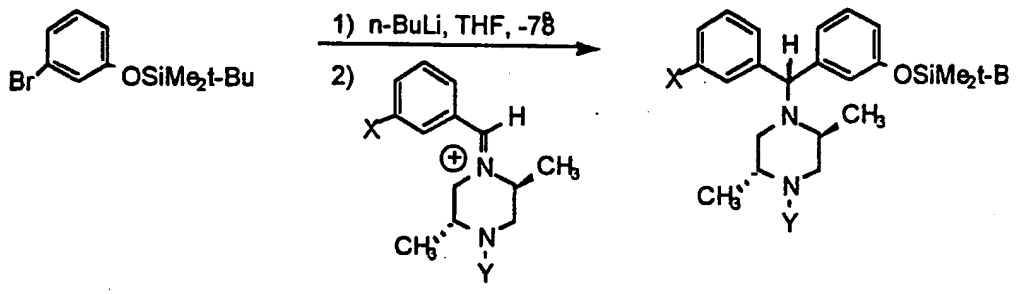


The intermediate could also be prepared via the benzophenone, which in turn could be obtained from an organometallic addition to 4-bromobenzonitrile:



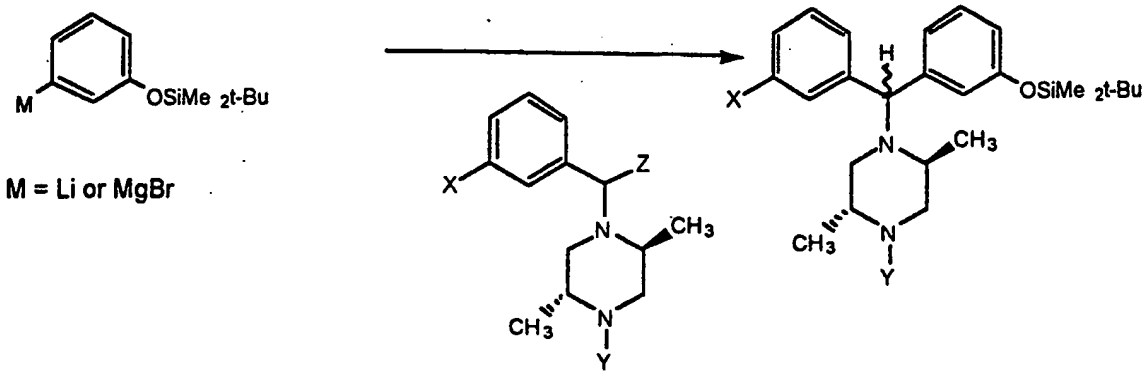
Other alternatives to intermediates involve condensation of an appropriately substituted piperazine with a carbonyl compound. Condensation with a benzaldehyde could provide an imminium salt that could add an aryllithium to provide benzhydryl piperazine compounds wherein X = $CONEt_2$, Y = $CH_2CH{=}CH_2$, or wherein X = Br, Y = $CH_2CH{=}CH_2$, as mixtures with their diastereomers, or protected precursors to those compounds.



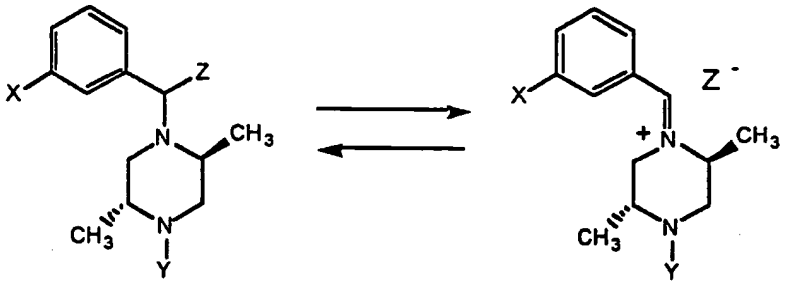


Similarly, reductive amination of the appropriate benzophenone with a suitable piperazine may provide the desired compounds directly.

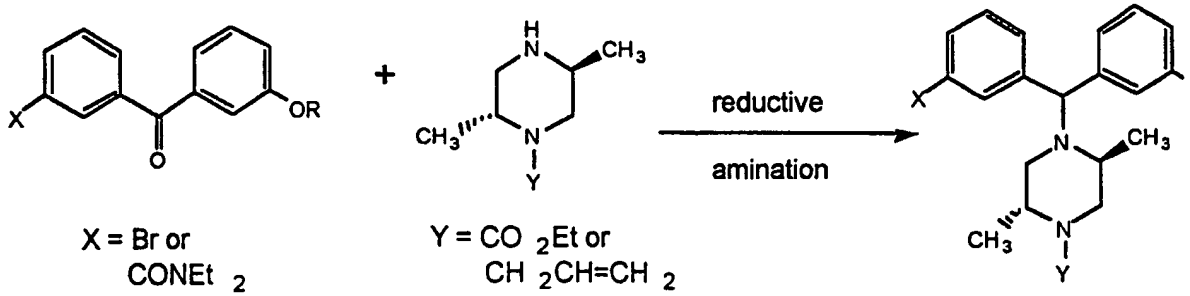
Similarly, a "masked imminium" compound, where Z is a suitable leaving group (e.g. benzotriazole or oxotitaniumtrichloride), may be treated with an arylmetal species (e.g. an aryllithium or an arylmagnesium bromide reagent),



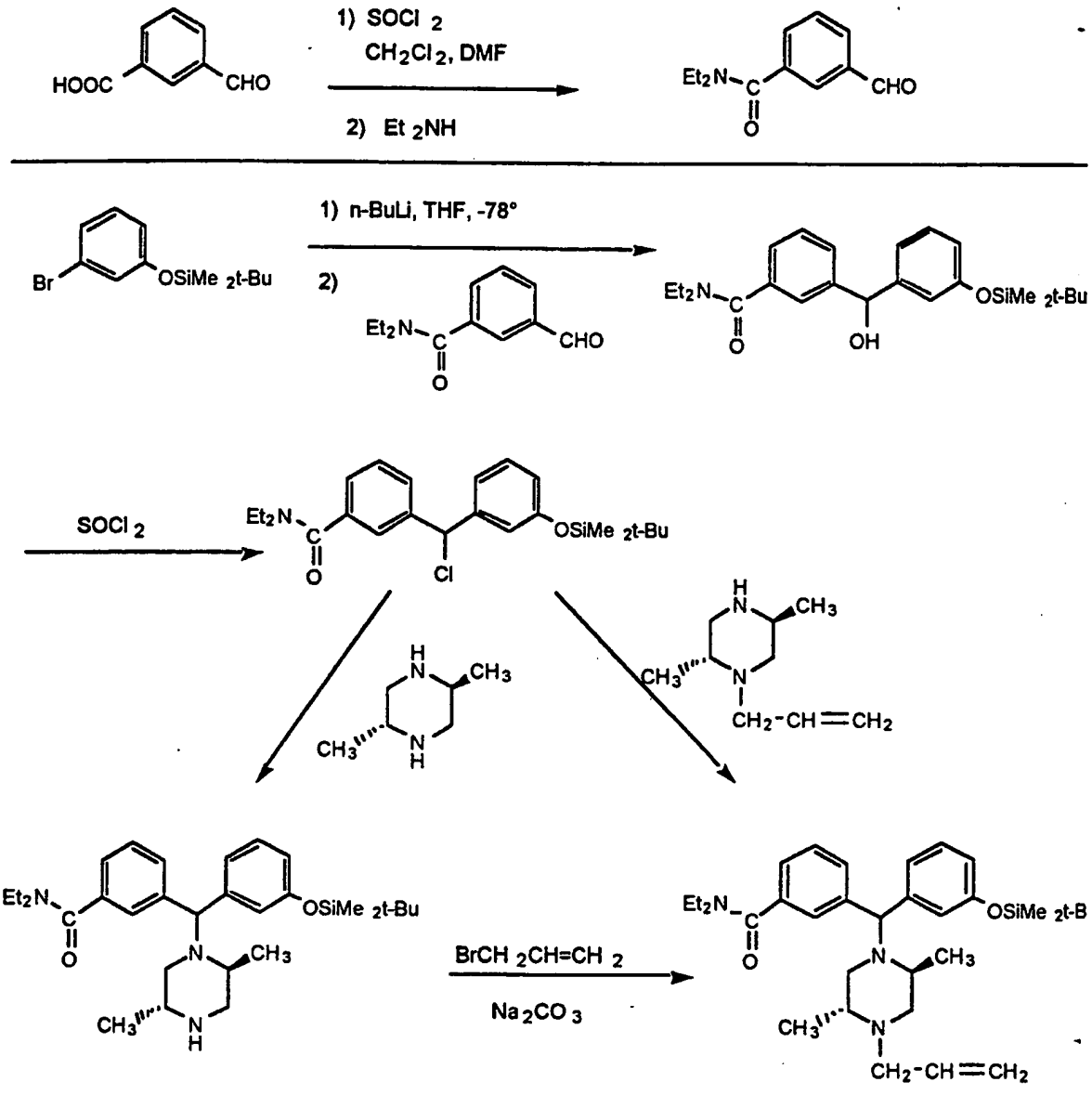
wherein the benzylpiperazine may dissociate to generate the requisite imminium ion *in situ*.

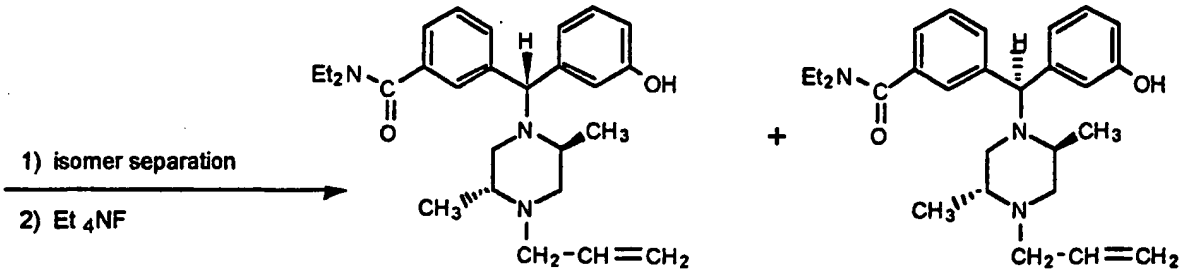


Similarly, reductive amination of the appropriate benzophenone with a suitable piperazine may provide the desired compounds directly.



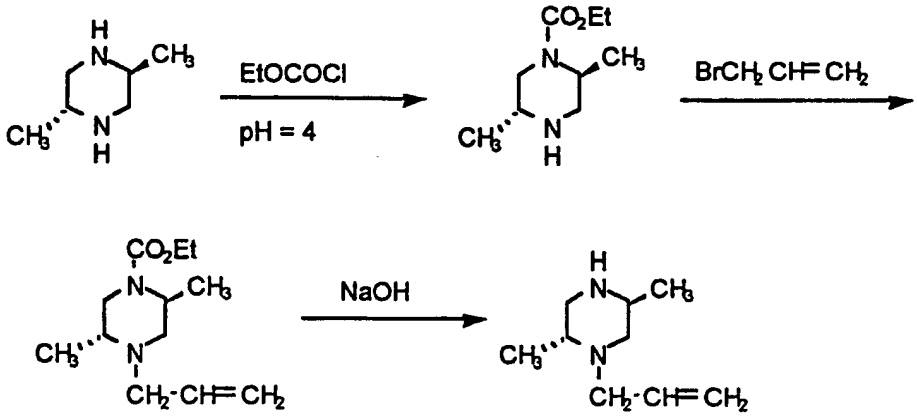
Compound (±)-I can also be synthesized by the alternative synthetic route set out below.





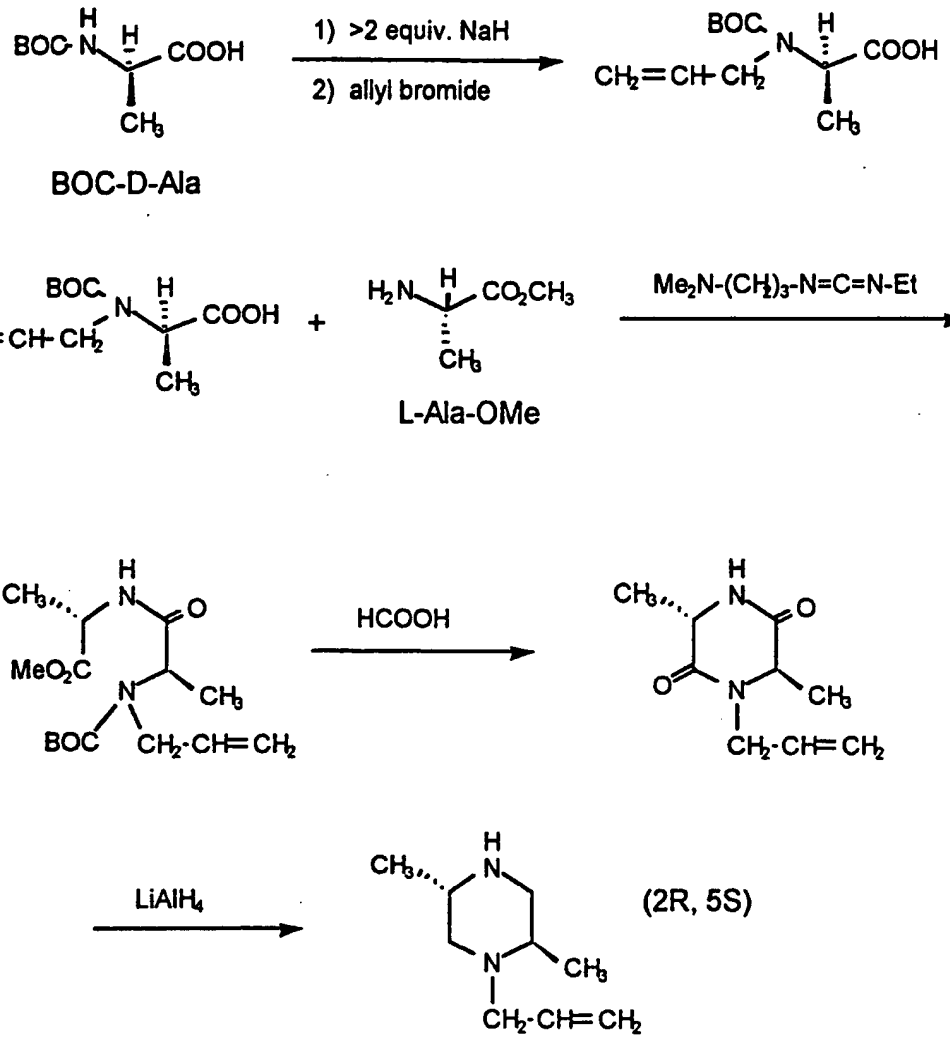
Compound (±)-I

The *trans*-1-allyl-2,5-dimethylpiperazine reactant utilized in the above synthesis scheme may suitably be formed by the following synthetic process.

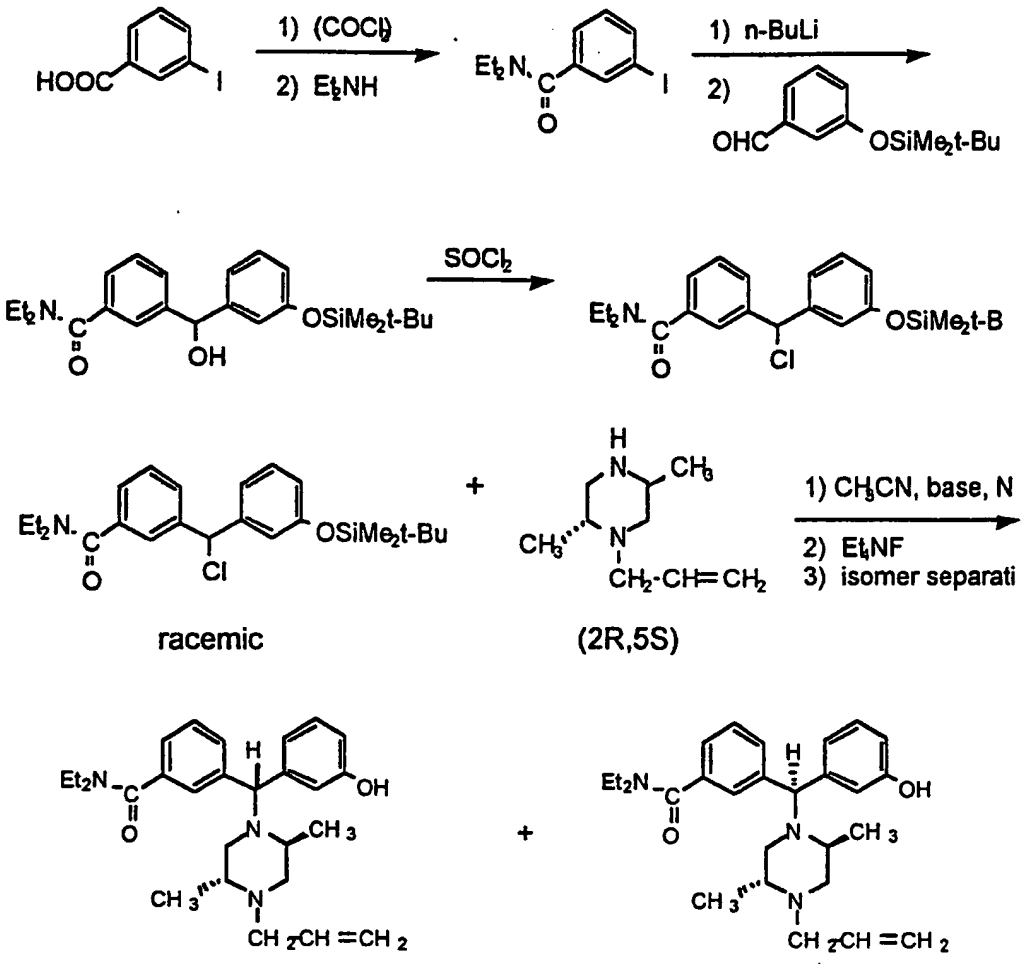


The racemic *trans*-1-allyl-2,5-dimethylpiperazine may be resolved into its constituent enantiomers by classical resolution with an enantiopure carboxylic acid to provide chiral intermediate (2R,5S)-1-allyl-2,5-dimethylpiperazine for the production of the (+)-antipode Compound I.

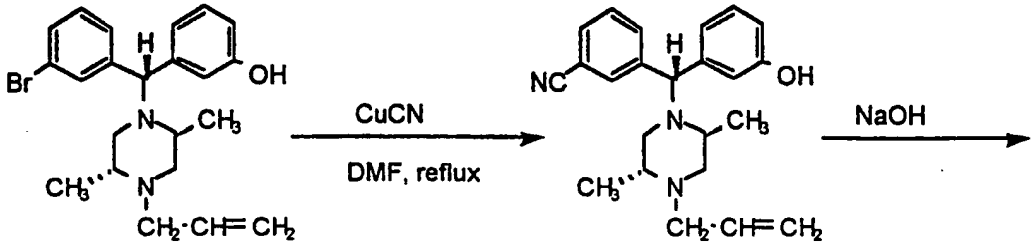
The (2R,5S)-1-allyl-2,5-dimethylpiperazine may also be made in enantiopure form, by the illustrative synthetic route outlined below.

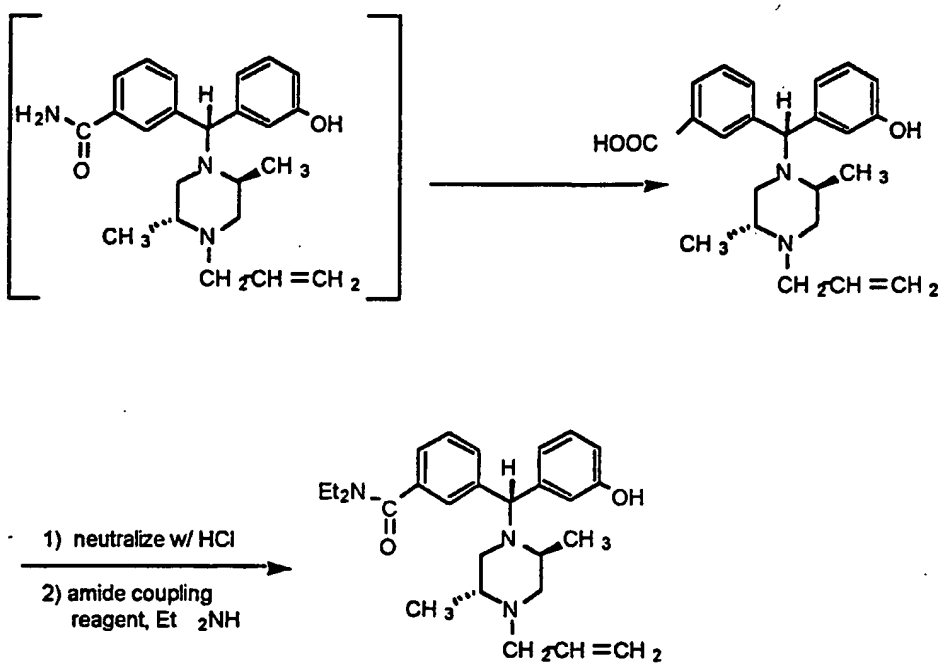


When the enantiopure (2R,5S)-1-allyl-2,5-dimethylpiperazine is treated with a racemic benzhydryl chloride, the resultant product is a mixture of two enantiopure diastereomers that can be separated by conventional methods such as chromatography or fractional crystallization.



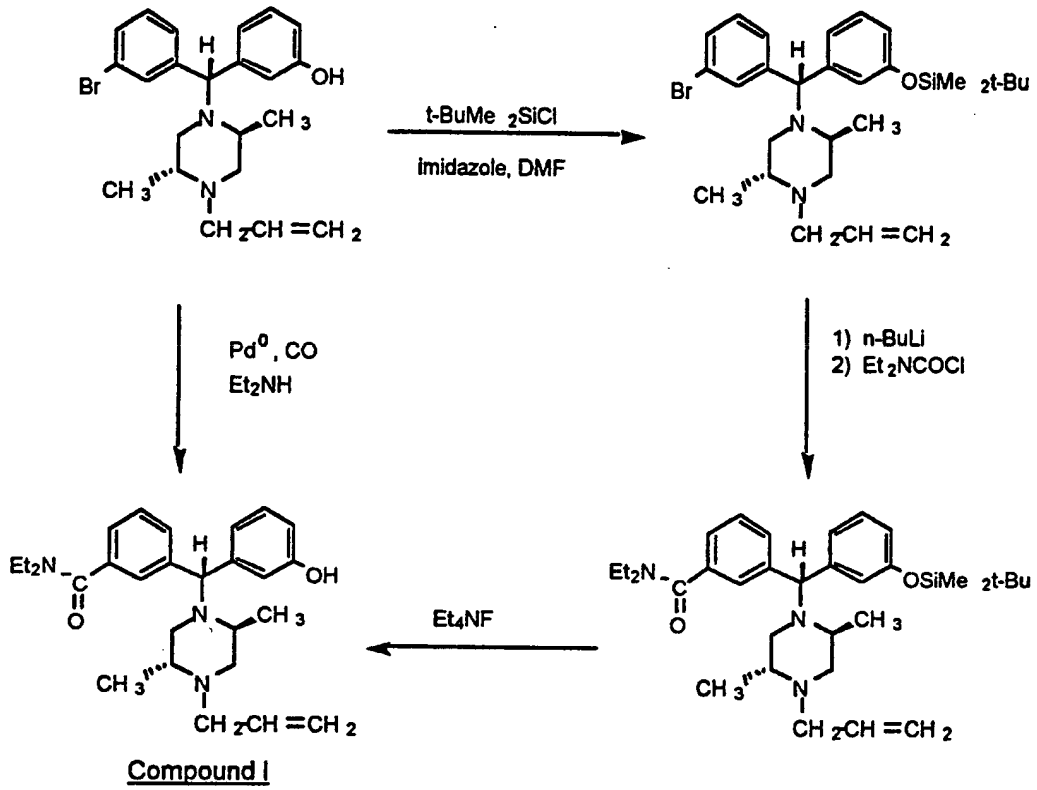
In addition to the foregoing, Compounds I or (±)-I may be synthesized via a nitrile synthesis route, utilizing cuprous cyanide as a nitrilation agent, as shown below.





Compound I

Alternative syntheses of Compound I from a corresponding halogenated compound are set out below.



Compound I

The foregoing have been illustratively set out as examples of synthetic techniques which may be usefully employed to form compounds such as Compounds I or (±)-I, as well as benzhydrylpiperazine compounds of the present invention, via corresponding or analogous reagents.

The features and advantages of the invention are more fully shown with respect to the following non-limiting examples.

Certain specifications and methods common to many of the following examples relating to chemical synthesis are described in the next paragraph.

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. All chemical reagents were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin,

unless otherwise specified. Commercial solvents were used without further purification except tetrahydrofuran, which was distilled from potassium metal. Nuclear magnetic resonance (NMR) spectra were variously obtained with Perkin-Elmer R-24, Varian XL-200, or XL-300 spectrometers. HPLC analyses were performed with a Waters liquid chromatography system equipped with a 700 Satellite WISP, 600E System Controller and a 991 Photodiode Array detector, with either a Cyclobond I column (4.6 x 250 mm, Advanced Separations Technologies, Whippany, New Jersey) or a μ-Bondapak C-18 column (125 Å, 3.9 x 300 mm, Waters Chromatography Division, Millipore Corporation, Milford, Massachusetts) at a flow rate of 1 ml/min. Analytical gas chromatography was performed on a Hewlett-Packard Series II instrument, Model 5890 with flame ionization detector using helium as the carrier gas (injector temperature, 225 °C; detector temperature, 250 °C). Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. Mass spectra were performed by Oneida Research Services, Whitesboro, New York. X-Ray crystallography was performed by Molecular Structure Corporation, College Station, Texas. Analytical thin layer chromatography was performed on Analtech glass plates pre-coated with silica gel GF (250 microns), and preparative thin layer chromatography on Analtech Uniplates pre-coated with silica gel GF (1000 and 2000 microns). Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia.

(REFERENCE) EXAMPLE 1

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N,N-diethylbenzamide

3-Iodobenzoic acid (55.5 g, 0.224 mol) was dissolved in tetrahydrofuran (220 mL) and oxalyl chloride (22 mL, 0.252 mol). Catalytic dimethylformamide (4 drops) was added, the solution was stirred at room temperature for 1 hour, and the solvent was removed under vacuum. The residue was dissolved in 220 mL petroleum ether (35-60 °C boiling range) and cooled to 0 °C in an ice bath. Diethylamine (55 mL, 0.532 mol) was then added dropwise over 15 minutes. The reaction mixture was stirred an additional 15 minutes in the ice bath, then diluted with ethyl acetate (100 mL) and washed with saturated sodium chloride solution (50 mL). The organic layer was separated, dried over magnesium sulfate, and concentrated *in vacuo* to approximately half of the original volume. The solution was then filtered through a small pad of silica gel, using ethyl acetate to wash the pad. All volatiles were removed *in vacuo*, and the product was dried under high vacuum to give 65.69 g (97%) of N,N-diethyl-3-iodobenzamide as an amber oil. NMR (300 MHz, $CDCl_3$): δ 1.11 (br s, 3H); 1.21 (br s, 3H); 3.23 (br s, 2H); 3.51 (br s, 2H); 7.13 (ddd, J_1= 0.8 Hz, J_2= 7.6 Hz, J_3= 7.6 Hz, 1H); 7.32 (ddd, J_1= 1.3 Hz, J_2= 1.3 Hz, J_3= 7.5 Hz, 1H); 7.71 (d, J=1.2 Hz, 1H); 7.72 (ddd, J_1= 1.3 Hz, J_2= 1.3 Hz, J_3= approx. 8.0 Hz (partially obstructed), 1H). Mass spectrum (Cl-CH_4) m/e: 304 (M+1, 100%). Calc. for $C_{11}H_{14}NOI$: C, 43.58; H, 4.65; N, 4.62; I, 41.86. Found: C, 43.68; H, 4.64; N, 4.64; I, 41.92.

3-Hydroxybenzaldehyde (70 g, 0.57 mol), tert-butyldimethylsilyl chloride (92 g, 0.61 mol), and imidazole (92 g, 1.35 mol) were combined in dimethylformamide (250 mL). The mixture was stirred at room temperature, under nitrogen, for 1 hour. The solution was poured into water (1.5 L) and extracted with 2 x 500 mL petroleum ether (35-60 °C boiling range). The organic solution was washed with saturated sodium chloride solution (100 mL), dried over magnesium sulfate, treated with silica gel (20 g), filtered, and concentrated *in vacuo*. The residue was dried further under high vacuum to yield 126.6 g (94%) of the air and light-sensitive 3-((tert-butyldimethylsilyl)oxy)benzaldehyde as an amber oil. NMR (300 MHz, $CDCl_3$): δ 0.22 (s, 6H); 0.99 (s, 9H); 7.10 (ddd, J_1= 1.2 Hz, J_2= 2.5 Hz, J_3= 7.9 Hz, 1H); 7.32 (dd, J_1= 1.5 Hz, J_2= 2.4 Hz, 1H); 7.39 (t, J= 7.8 Hz, 1H); 7.47 (ddd, J_1= 1.3 Hz, J_2= 1.3 Hz, J_3= 7.6 Hz, 1H); 9.95 (s, 1H).

Mass spectrum (Cl-CH_4) m/e: 237 (M+1, 100%). Calculated for $C_{13}H_{20}O_2Si$: C, 66.05; H, 8.53. Found: C, 65.95; H, 8.56.

n-Butyllithium in hexanes (280 mL of a 2.5M solution) was added via a dropping funnel to tetrahydrofuran (1.4 L) at -78 °C, under nitrogen. When the n-butyllithium solution had cooled back to -78 °C, a solution of N,N-diethyl-3-iodobenzamide (106 g, 0.35 mol) in tetrahydrofuran (350 mL) was added slowly over 20 minutes. The internal temperature rose to -65 °C during the addition. After the addition was complete, the solution was stirred for 10 minutes, and a solution of 3-((tert-butyldimethylsilyl)oxy)benzaldehyde (88 g, 0.37 mol) in tetrahydrofuran (90 mL) was added slowly over 7 minutes. The reaction mixture was stirred for an additional 5 minutes at -78 °C and allowed to warm to -10 °C. The mixture was poured into 875 mL petroleum ether (35-60 °C boiling range) and sodium phosphate dibasic solution (350 mL of 2M aqueous solution), shaken, and the organic phase separated. The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in an ethyl acetate-petroleum ether mixture (1:3, 90 mL), placed on a column of silica gel (1 kg), and washed with ethyl acetate-petroleum ether (1:3) to remove fast eluting impurities. Elution with ethyl acetate yielded, after *in vacuo* concentration, 115.9 g (80%) of 3-(3-((tert-butyldimethylsilyl)oxy)-α-hydroxybenzyl)-N,N-diethylbenzamide as a viscous amber oil. NMR (300 MHz, DMSO-d_6): δ 0.13 (s, 6H); 0.92 (s, 9H); 0.98 (br s, 3H); 1.11 (br s, 3H); 3.10 (br s, 2H); 3.39 (br s, 2H); 5.69 (d, J=4.1 Hz, 1H); 5.96 (d, J=4.2 Hz, 1H); 6.68 (dd, J_1= 1.9 Hz, J_2= 7.7 Hz, 1H); 6.84 (s, 1H); 6.97 (d, J= 7.7 Hz, 1H); 7.16 (d, J= approx. 8 Hz (partially obscured), 1H); 7.17 (t, J= 7.7 Hz, 1H); 7.28 (s, 1H); 7.35 (t, J= 7.8 Hz, 1H); 7.42 (d, J= 7.6 Hz, 1H). Mass spectrum (Cl-CH_4) m/e: 414 (M+1, 11%), 178 (32%). Calc. for $C_{24}H_{35}NO_3Si$: C, 69.69; H, 8.53; N, 3.39. Found: C, 69.65; H, 8.56; N, 3.40.

A 12 L, 3-necked round bottom flask was charged with *trans*-2,5-dimethylpiperazine (767 g, 6.72 mol), which had been recrystallized from toluene to mp=115-119 °C, and 600 mL of water. The flask was cooled in an ice bath and a solution of methanesulfonic acid (1290 g, 13.4 mol) in 600 mL of water was added slowly with stirring and cooling to maintain the temperature below 40 °C. The solution was cooled to 20 °C and 800 mL of ethanol was added. A 500 mL addition funnel was filled with 60% aqueous potassium acetate from a 2 L reservoir of the solution, and potassium acetate was added to the reaction flask to adjust the pH to 4.0. A second addition funnel was charged with a solution of ethyl chloroformate (642 mL, 6.71 mol) in 360 mL of tetrahydrofuran.

The ethyl chloroformate and potassium acetate solutions were simultaneously added dropwise with adjustment of rate to maintain the reaction solution at pH 4.0 ±0.1, with cooling as necessary to maintain temperature at 25 °C. After addition of the ethyl chloroformate was complete, the reaction was stirred for 1 hour with continued addition of potassium acetate solution to maintain a pH of 4.0. The organic solvents were removed by distillation under vacuum. The remaining aqueous solution was washed with 1500 mL of ethyl acetate to remove any bis-carbamate impurity. The ethyl acetate wash was extracted with two 500 mL portions of 1 M hydrochloric acid to recover desired product. The acid extracts were combined with the original aqueous solution and the pH was adjusted to 11 by addition of 10 M sodium hydroxide, with cooling to maintain temperature below 40 °C. The aqueous solution was extracted with two 1500 mL portions of ethyl acetate, the combined extracts were dried over magnesium sulfate, and the solvent was removed to give 927 g (74%) ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate as a yellow oil.

A mixture of ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate (643 g, 3.45 mol), allyl bromide (328 mL, 3.80 mol), and sodium carbonate (440 g, 4.15 mol) in 2500 mL of acetonitrile was heated at reflux for 1.5 hours. The reaction was cooled to room temperature, filtered, and the solvent removed under vacuum. The residue was dissolved in 4000 mL of dichloromethane and washed with two 500 mL portions of 1 M sodium hydroxide. The dichloromethane solution was dried over magnesium sulfate and the solvent was removed to give 630 g (81%) of ethyl *trans*-4-allyl-2,5-dimethyl-1-piperazinecarboxylate as an oil.

Ethyl *trans*-4-allyl-2,5-dimethyl-1-piperazinecarboxylate (630 g, 2.78 mol) was added to a solution of 87% potassium hydroxide pellets (2970 g, 46 mol) in 4300 mL of 95% ethanol and heated at reflux for 1.5 hours. Carbon dioxide evolution was observed for the first 0.5 - 1 hour of heating. The reaction was cooled below reflux temperature and 2000 mL of toluene was carefully added. Ethanol was removed by azeotropic distillation at 105 °C, while adding an additional 4000 mL of toluene to the reaction flask during the course of the distillation. After collection of 9000 mL of distillate, the reaction was cooled to 100 °C and 1000 mL of toluene was carefully added. The solution was slowly cooled to 5 °C and maintained at 5 °C for 30 minutes. The solution was filtered, and the filter cake was washed with an additional 1500 mL of toluene. The filtrate was washed with 1000 mL of water, dried over magnesium sulfate, and the solvent was removed to give 296 g (69%) of *trans*-1-allyl-2,5-dimethylpiperazine as a dark liquid. NMR (300 MHz, DMSO-

d_6): δ 0.87 (d, J=6.3 Hz, 3H); 0.92 (d, J=6.3 Hz, 3H); 1.63 (t, J=11 Hz, 1H); 2.05 (m, 1H); 2.30 (t, J=11 Hz, 1H); 2.6-2.8 (m, 4H); 3.33 (dd, J_1= 5 Hz, J_2= 14 Hz, 1H); 5.09 (d, J=8.7 Hz, 1H); 5.13 (d, J=14 Hz, 1H) 5.8 (m, 1H).

Di-*p*-toluoyl-D-tartaric acid (Schweizerhall, Inc., South Plainfield, New Jersey) (1.25 Kg, 3.2 mol) was dissolved in hot (~60 °C) 95% ethanol (16 L) and racemic *trans*-1-allyl-2,5-dimethylpiperazine (500 g, 3.2 mol) was added in several portions (caution: exothermic). The hot solution was seeded with crystals of the diastereoisomerically pure salt (obtained from a previous small-scale resolution) and cooled to room temperature over 2-3 hours. The solution was slowly stirred for 2 days at room temperature. The resulting salt was collected by filtration, washed twice with 95% ethanol, and dried under vacuum to give 826.5 g of a white solid (47%). The process was repeated with a second batch of the di-*p*-toluoyl-D-tartaric acid and racemic *trans*-1-allyl-2,5-dimethylpiperazine to give 869 g (50%).

The total of 1695 g of salt was divided into three batches and each batch was recrystallized twice in the following fashion. The salt was dissolved in refluxing 95% ethanol (~2.7 L/100 g of salt), and approximately half of the ethanol was removed by distillation. (Note: vigorous stirring was necessary during distillation to prevent crystallization on the vessel wall.) The hot solution was seeded with crystals of the pure diastereomeric salt, cooled to room temperature, and stirred slowly for 2 days before collecting the salt by filtration. (Note: a subsequent experiment suggested that crystallization time can be reduced from 2 days to 8 hours.) The total amount recovered was 1151 g. The salt was dissolved in 3 L of 2 M aqueous sodium hydroxide, and the aqueous solution was extracted with four 1 L portions of dichloromethane. The organic extracts were combined, dried over sodium sulfate, and solvent removed by rotary evaporation (temperature < 20 °C) to give 293 g (29% based on racemic weight) of (2R,5S)-1-allyl-2,5-dimethylpiperazine as a clear oil. $[\alpha]_D^{20}$ = -55.1° (abs. ethanol, c=1.2). The trifluoroacetamide of the product was prepared with trifluoroacetic anhydride and analyzed by chiral capillary gas chromatography (Chiraldex B-PH column, 20 m x 0.32 mm, Advanced Separation Technologies Inc., Whippany, NJ, 120 °C) indicating an enantiopurity of >99% ee (retention time of desired enantiomer, 11.7 min; other enantiomer, 10.7 min).

3-(3-((tert-Butyldimethylsilyl)oxy)-a-hydroxybenzyl)-N,N-diethylbenzamide (115.9 g, 0.280 mol) was dissolved in tetrahydrofuran (560 mL) and thionyl chloride (24.5 mL, 0.336 mol) was added. The reaction was noticeably exothermic. The mixture was stirred for 15 minutes and concentrated *in vacuo* (cautiously at first, due to rapid gas evolution). After all volatiles were removed, the crude 3-(3-((tert-butyldimethylsilyl)oxy)-a-chlorobenzyl)-N,N-diethylbenzamide was dissolved in acetonitrile (560 mL). Sodium iodide (42 g, 0.280 mol), diisopropylethylamine (73 mL, 0.42 mol), and (2R,5S)-1-allyl-2,5-dimethylpiperazine (52.5 g, 0.280 mol) were added. The mixture was stirred at reflux, under nitrogen, for 2.5 hours. The acetonitrile was removed by distillation, under nitrogen, over the next hour. After cooling, the reaction mixture was poured into ethyl acetate (1.1 L) and potassium carbonate solution (350 mL of a 2M aqueous solution), and shaken. The organic phase was separated, dried over solid potassium carbonate, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate-petroleum ether (1:1, 150 mL), and placed on a column of silica gel (3 kg). Elution with ethyl acetate-petroleum ether (1:1) afforded the desired isomer as the first of the two epimers to elute. The eluate solution was concentrated to a small volume and allowed to stand for 12 hours. A crystalline impurity that precipitated was removed by filtration, and the filtrate was concentrated to dryness.

The residue was dissolved in tetrahydrofuran-petroleum ether (1:1, 125 mL) and extracted with 350 mL of 0.75 M hydrochloric acid. The aqueous phase, containing the desired product, was stirred at room temperature for 24 hours to cleave the silyl ether. The solution was then washed with 1:1 ethyl acetate-petroleum ether (2 x 100 mL). The aqueous solution was stirred with ethyl acetate (100 mL) while solid sodium bicarbonate (38 g) was added portionwise, with caution (vigorous gas evolution). After 15 minutes of additional stirring, the layers were separated and the aqueous layer extracted again with ethyl acetate (100 mL). The two ethyl acetate portions were combined, dried over sodium sulfate, concentrated *in vacuo*, and dried under high vacuum to yield 37.3 g (30%) of (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide as an off-white solid. $[\alpha]_D^{20}$ = +20° (methanol, c=2). NMR (400 MHz, DMSO-d_6): δ 0.91 (d, J= 6.2 Hz, 3H); 0.99 (br s, 3H); 1.05 (d, J= 6.2 Hz, 3H); 1.09 (br s, 3H); 1.84 (dd, J_1= 7.3 Hz, J_2= 10.9 Hz, 1H); 2.06 (dd, J_1= 7.3 Hz, J_2= 10.9 Hz, 1H); 2.48 (m, 1H); 2.51 (dd, J_1= 2.7 Hz, J_2= 10.9 Hz, 1H); 2.58 (br s, 1H); 2.70 (dd, J_1= 2.7 Hz, J_2= 10.9 Hz, 1H); 2.81 (dd, J_1= 7.0 Hz, J_2= 13.9 Hz, 1H); 3.12 (br s, 2H); 3.15 (dd, J_1= 5.1 Hz, J_2= 13.9 Hz, 1H); 3.38 (br s, 2H); 4.97 (br s, 1H); 5.07 (d, J= 10.2 Hz, 1H), 5.14 (d, J= 16.9 Hz, 1H); 5.70-5.82

(m, 1H); 6.64 (dd, J_1= 2.1 Hz, J_2= 8.0 Hz, 1H); 6.65 (s, 1H); 6.68 (d, J= 7.7 Hz, 1H); 7.11 (t, J= 8.0 Hz, 1H); 7.14 (d, J= 7.6 Hz, 1H); 7.30 (s, 1H); 7.33 (t, J= 7.6 Hz, 1H); 7.39 (d, J= 8.0 Hz, 1H); 9.31 (s, 1H). Mass spectrum (CI-CH_4) m/e: 436 (M+1, 53%). Calc. for $C_{27}H_{37}N_3O_2$ 0.5 H_2O: C, 72.94; H, 8.61; N, 9.45. Found: C, 73.00; H, 8.57; N, 9.40. The free amine (32.2 g) was dissolved in 200 mL of absolute ethanol and titrated with ethanolic hydrogen chloride (7 M and 1 M) to a pH of 3.95. The solvent was removed and the residue was redissolved in 50 mL of dichloromethane. Diethyl ether (900 mL) was added with vigorous stirring to precipitate a gummy product which solidified upon stirring overnight under nitrogen. The product was collected by filtration and dried under vacuum at 55 °C to give 33.06 g (91% recovery) of the monohydrochloride salt. Calc. for $C_{27}H_{37}N_3O_2$ HCl H_2O: C, 66.17; H,8.23; N, 8.57; Cl, 7.23. Found: C, 66.40; H,8.17; N, 8.48; Cl, 7.28.

EXAMPLE 2

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-methyl-N-phenylbenzamide

A mixture of 1400 g (8.1 mol) of 3-bromophenol, 1218 g (8.1 mol) of tert-butylchlorodimethylsilane and 1376 g (20.2 mol) of imidazole in 1600 mL of N,N-dimethylformamide was stirred at room temperature under nitrogen for 18 hours. The reaction mixture was poured into pH 8 aqueous buffer solution and extracted with diethyl ether. The ether extracts were washed with water and brine, dried over sodium sulfate, and the solvent was evaporated under vacuum to give 2314 g of crude 3-bromophenyl tert-butyldimethylsilyl ether as an orange oil. NMR ($CDCl_3$, 200 MHz) d: 0.2 (s, 6H); 0.95 (s, 9H); 6.8 (m, 1H); 7.0-7.1 (m, 3H).

The silyl ether (1771 g, 6.17 mol) was dissolved in 4 L of dry tetrahydrofuran, dried further over molecular sieves, then transferred to a 12 L reaction flask under nitrogen and cooled to -78 °C. n-Butyllithium (2400 mL of a 1.6M solution in hexane) was added, while stirring under nitrogen, at a rate to keep the temperature below -70 °C. Stirring was continued at -78 °C for 2 hours. A solution of 3-bromobenzaldehyde (1119 g, 6.05 mol) in 600 mL of dry tetrahydrofuran was added at a rate to keep the reaction temperature below -70 °C. After stirring for 2 hours at -78 °C, the reaction was quenched with 1400 mL of saturated aqueous ammonium chloride and allowed to

warm to room temperature. The mixture was filtered to remove solids and the layers were separated. The organic phase was washed with brine, dried over sodium sulfate and evaporated to give 2500 g of crude α-(3-bromophenyl)-3-(tert-butyldimethylsilyloxy)-benzyl alcohol as a yellow oil. Chromatography on silica gel of 1 kg of the crude product with hexane:dichloromethane (gradient from 90:10 to 75:25, followed by dichloromethane:ethyl acetate/90:10) gave 692.3 g of α-(3-bromophenyl)-3-(tert-butyldimethylsilyloxy)benzyl alcohol as a yellow oil. NMR ($CDCl_3$, 200 MHz) δ: 0.2 (s, 6H); 0.95 (s, 9H); 2.3 (br s, 1H); 5.7 (s, 1H); 6.75 (d, J=8 Hz, 1H); 6.8 (s, 1H); 6.9 (d, J=8 Hz, 1H); 7.2 (m, 2H); 7.3 (d, J=8 Hz, 1H); 7.4 (d, J=8 Hz, 1H); 7.5 (s, 1H).

Thionyl chloride (38 mL, 0.51 mol) was added dropwise to a solution of the benzhydryl alcohol (160 g, 0.41 mol) in 1 L of dichloromethane and the mixture was stirred overnight at room temperature. The solvent was removed under vacuum, the residue was redissolved in toluene, and the solvent was again removed under vacuum to eliminate excess thionyl chloride to give crude α-(3-bromophenyl)-3-(tert-butyldimethylsilyloxy)benzyl chloride as a brown oil. NMR ($CDCl_3$, 200 MHz) δ: 0.2 (s, 6H); 0.95 (s, 9H); 6.0 (s, 1H); 6.8-7.0 (m, 3H); 7.2-7.6 (m, 5H).

A mixture of the benzhydryl chloride and (-)-(2R,5S)-1-allyl-2,5-dimethylpiperazine (137.6 g, 0.89 mol, from Example 1, *infra*) in 1500 mL of acetonitrile was heated at reflux for 48 hours, concentrated *in vacuo*, and the residue dissolved in ethyl acetate. The mixture was washed with 0.25 M aqueous sodium hydroxide, dried over sodium sulfate and concentrated *in vacuo* to give 202.6 g of dark oil, which was dissolved in acetonitrile (1 L) and treated with tetraethylammonium fluoride dihydrate (88.9 g, 0.48 mol). After stirring at room temperature overnight, the solvent was removed under vacuum. The residue was dissolved in dichloromethane (2 L), washed with pH 8 aqueous buffer solution, dried over sodium sulfate and concentrated down to a dark oil which was stirred in acetonitrile (700 mL) at 25 °C for 72 hours to produce a tan precipitate. Recrystallization from acetonitrile (2 L) gave 35.3 g of a single diastereomer: (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-bromobenzyl)phenol as a white solid. NMR (DMSO-d_6, 200 MHz) δ: 0.95 (d, J=6 Hz, 3H); 1.03 (d, J=6 Hz, 3H); 1.8 (dd, J_1=6 Hz, J_2=10 Hz, 1H); 2.1 (dd, J_1=6 Hz, J_2=10 Hz, 1H); 2.4-2.6 (m, 3H); 2.7 (d, J=11 Hz, 1H); 2.8 (dd, J_1=7 Hz, J_2=14 Hz, 1H); 3.2 (dd, J_1=6 Hz, J_2=13 Hz, 1H); 4.9 (s, 1H); 5.1 (d, J=10 Hz, 1H); 5.2 (d, J=18 Hz, 1H); 5.7-5.9 (m, 1H); 6.6-6.8 (m, 3H); 7.0-7.4 (m, 4H); 7.55 (s, 1H); 9.35 (s, 1H). The mother liquor was evaporated to give 127 g of a brown solid. A portion (11 g) of this solid was purified by

chromatography on silica gel with dichloromethane:ethanol (0-2.5%). The first isomer to elute from the column was collected to give 2.32 g of 3-((αS)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-bromo-benzyl)phenol as a light yellow solid. NMR (DMSO-d_6, 200 MHz) δ: 0.95 (d, J=6 Hz, 3H); 1.05 (d, J=6 Hz, 3H); 1.85 (dd, J_1= 7 Hz, J_1= 9 Hz, 1H); 2.1 (dd, J_1=6 Hz, J_2=9 Hz, 1H); 2.5 (m, 3H); 2.7 (dd, J_1=2 Hz, J_2=8 Hz, 1H); 2.9 (dd, J_1=7 Hz, J_2=7 Hz, 1H); 3.1 (dd, J_1=5 Hz, J_2=9 Hz, 1H); 4.95 (s, 1H); 5.1 (d, J=10 Hz, 1H); 5.2 (d, J=17 Hz, 1H); 5.8 (m, 1H); 6.6 (d, J=8 Hz, 1H); 6.8 (m, 2H); 7.1 (t, J=8 Hz, 1H); 7.3 (m, 2H); 7.5 (m, 2H); 9.3 (s, 1H).

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-bromobenzyl)phenol (147.3 g, 0.355 mol) was dissolved in 1 L of N-methyl-2-pyrrolidinone with cuprous cyanide (63.6 g, 0.71mol), and the reaction was heated at 170 °C for 30 hours. The reaction was cooled to room temperature and poured into 7 L of aqueous 14% sodium cyanide. The mixture was stirred overnight and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water, dried over sodium sulfate and concentrated *in vacuo* to give 133.3 g of a brown solid. Chromatography on silica gel with ethanol (2-7%) in dichloro-methane gave 97.8 g of crude (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzonitrile. Recrystallization from acetonitrile gave 74.2 g (58%) pure (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzonitrile as a white solid.

The benzonitrile (78.8 g, 0.22 mol) was combined with 60 g of sodium hydroxide pellets in 1 L of 95% ethanol and heated at reflux for 72 hours. The mixture was concentrated *in vacuo* to remove ethanol. The residue was dissolved in water and the resulting solution was adjusted to pH 5 with concentrated hydrochloric acid. The solvent was removed *in vacuo* to give 138.8 g of the 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid as a mixture with sodium chloride. A portion (5.0 g) of the crude acid was stirred with 50 mL of water. The resulting slurry was filtered, the solid in the filter was washed three times with water then dried under vacuum for three hours to give 2.02 g of (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid as a light beige solid. NMR (DMSO-d_6, 200 MHz) δ: 0.95 (d, J=6 Hz, 3H); 1.1 (d, J=6 Hz, 3H); 1.9 (ddd, J_1= 3 Hz, J_2= 7 Hz, J_3= 10 Hz, 1H); 2.1 (dd, J_1=8 Hz, J_2=10 Hz, 1H); 2.5 (m, 2H); 2.7-2.9 (m, 2H); 3.2 (m, 2H); 5.05 (d, J=12 Hz, 1H); 5.2 (d, J=18 Hz, 1H); 5.8 (m, 1H); 6.7 (m, 3H); 7.1 (t, J=8 Hz, 1H); 7.4 (t, J=8 Hz, 1H); 7.65 (d, J=8 Hz, 1H); 7.8 (d, J=8 Hz, 1H); 8.0 (s, 1H); 9.4 (s, 1H). $[\alpha]_D^{20}$ = +4.1° (0.1 M aqueous sodium hydroxide, c=1.09).

Calc. for $C_{23}H_{28}N_2O_3$ 0.75 H_2O: C, 70.12; H, 7.55; N, 7.11. Found: C, 70.23; H, 7.35; N, 7.10. Mass spectrum (Cl-CH_4) m/e: 381 (M+1, 35%); 380 (M, 2%); 227 (28%); 155 (100%); 153 (83%).

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid (25.9 g of a 50% by weight mixture with sodium chloride, 34.0 mmol) was dissolved in 40 mL of dimethylformamide with 12.8 g (84.9 mmol) of tert-butylchlorodimethylsilane and 11.5 g (169.1 mmol) of imidazole and stirred overnight at room temperature. The reaction solution was poured into 500 mL of ice water and extracted with 500 mL of diethyl ether. The ether extract was washed twice with 250 mL of water, and then with 125 mL of saturated sodium chloride solution. The ether solution was dried over sodium sulfate and the solvent was removed to give 20.8 g of crude tert-butyldimethylsilyl 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)-benzoate.

The crude silyl ether-silyl ester (20.7 g, ≤33.9 mmol based on the previous reaction) was dissolved in 60 mL of dichloromethane and cooled to 0 °C under nitrogen. Oxalyl chloride (3.7 mL, 42.4 mmol) was added dropwise. While maintaining the bath temperature at 0 °C, catalytic dimethylformamide (10 drops) was added slowly. Evolution of gas was evident during the addition of dimethylformamide. The bath temperature was maintained at 0 °C for 30 minutes, then allowed to warm to room temperature. The solution was stirred at room temperature, under nitrogen for 24 hours. All of the volatiles were removed by evaporation under reduced pressure to give 29.76 g of crude 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride as a yellow-brown solid. The crude acid chloride was used without purification.

Benzamide-Formation Method

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride (2.33 g. crude, approx-imately 1.44 g. actual compound, 2.81 mmol based on 3-((αR)-α-((2S, 5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid) was dissolved in 12 mL of dichloromethane at room temperature under nitrogen. Triethylamine (0.5 mL) was added to the solution. N-methylaniline (0.46 mL, 4.3 mmol) was added dropwise to the solution (exothermic), and the reaction was stirred overnight at

room temperature. All volatiles were removed by evaporation under reduced pressure to provide a gummy brown solid.

This crude solid was dissolved in acetonitrile (8 mL) under nitrogen at room temperature. Tetraethylammonium fluoride hydrate (1.19 g, 6.42 mmol) was added and the solution was stirred for 1 hour at room temperature. After removal of solvent, the residue was purified by chromatography on silica gel (4 cm x 12 cm) with 0.5-2% ethanol in dichloromethane to give 0.368 g (28% over 4 steps from 3-((aR)-a-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid) of (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-N-methyl-N-phenylbenzamide as a light yellow solid. NMR (300 MHz, DMSO-d_6): δ 0.89 (d, J=6.0 Hz, 3H); 0.96 (d, J=6.0 Hz, 3H); 1.66 (dd, J_1=7.3 Hz, J_2=11.4 Hz, 1H); 2.01 (dd, J_1=7.8 Hz, J_2= 10.6 Hz, 1H); 2.26 (br d, J=10.6 Hz, 1H); 2.37-2.54 (m, 2H); 2.66 (br d, J=11.0 Hz, 1H); 2.82 (dd, J_1=7.0 Hz, J_2= 13.9 Hz, 1H); 3.17 (dd, J_1=4.8 Hz, J_2= 13.9 Hz, 1H); 3.34 (s, 3H); 4.77 (s, 1H); 5.10 (d, J=10.1 Hz, 1H); 5.16 (d, J=17.3 Hz, 1H); 5.70-5.82 (m,1H); 6.41 (d, J=7.4 Hz, 1H); 6.54 (s, 1H); 6.64 (d, J=8.0 Hz, 1H); 7.05-7.26 (m, 10H); 9.31 (s, 1H). Mass spectrum (CI-CH_4) m/e: 470 (M+1, 100%), 376 (81%), 316 (45%), 153 (97%). $[\alpha]_D^{20}$ = + 12.3° (ethanol, c= 1.2). The free amine (0.339 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.0 followed by precipitation with diethyl ether from dichloromethane to give 0.321 g (88% recovery) of the monohydrochloride salt as a hygroscopic light yellow powder. Calc. for $C_{30}H_{35}N_3O_2$ HCl H_2O: C, 68.75; H, 7.31; N, 8.02; Cl, 6.76. Found: C, 68.86; H, 7.42; N, 8.00; Cl, 6.84.

EXAMPLE 3

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-(4-fluorophenyl)-N-methylbenzamide

Following a general literature procedure for reductive alkylation (Krishnamurthy, S. Tetrahedron Lett. **1982**, 23, 3315) acetic-formic anhydride was prepared by slowly adding formic acid (7.5 mL) to acetic anhydride at 0 °C. After stirring for 5 minutes at 0 °C, the mixture was heated at 55 °C for 1.75 hours under nitrogen. The mixture was cooled to 0 °C and used without

purification. 4-Fluoroaniline (3.1 mL, 32.8 mmol) in tetrahydrofuran (10 mL) was added to acetic-formic anhydride (12.5 mL, 88 mmol) at 0 °C. The reaction was stirred for 25 minutes and the volatiles were removed under vacuum to provide the formamide as a brown solid. A portion of the crude solid (2.39 g, 17.2 mmol) was dissolved in tetrahydrofuran (8 mL) and cooled to 0 °C. Borane in tetrahydrofuran (40 mL of a 1.0 M solution) was added dropwise. Gas evolution was evident during the first half of the addition. After the addition, the solution was heated to reflux for 3 hours. The solution was cooled to 0 °C and methanol (10 mL) was added carefully. After stirring for 10 minutes, ethanolic hydrogen chloride (7 mL of a 7.1 M solution) was added and the reaction was stirred overnight. After removal of all volatiles *in vacuo*, crude N-methyl-4-fluoroaniline was obtained as a light purple solid. NMR (200 MHz, DMSO-d_6): δ 2.65 (s, 3H); 5.54 (s, 1H); 6.51 (dd, J_1=4.7 Hz, J_2=8.8 Hz, 2H); 6.93 (dd, J_1=8.9 Hz, J_2=8.8 Hz, 2H).

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl) benzoyl chloride (Example 2, *infra*, 2.08 g. crude, approximately 1.29 g actual compound, 2.51 mmol based on 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-benzoic acid) was dissolved in 8 mL of dichloromethane at room temperature under nitrogen. Triethylamine (0.5 mL) was added to the solution. Then 4-fluoro-N-methylaniline (0.478 mg, 3.82 mmol) in dichloromethane (5 mL) was added dropwise to the solution (exothermic), and the reaction was stirred overnight at room temperature. All volatiles were removed by evaporation under reduced pressure to provide a gummy yellow-brown solid.

The crude solid was dissolved in acetonitrile (8 mL) under nitrogen at room temperature. Tetraethylammonium fluoride hydrate (1.06 g, 5.7 mmol) was added and the solution was stirred overnight at room temperature. After removal of solvent, the residue was purified by chromatography on silica gel (4 cm x 14 cm) with 0.25-3.5% ethanol in dichloromethane to give 0.419 g (34% over 4 steps from 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid) of (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-N-(4-fluorophenyl)-N-methyl-benzamide as a yellow powder. NMR (300 MHz, DMSO-d_6): δ 0.88 (d, J=6.0 Hz ,3H); 0.96 (d, J=6.0 Hz, 3H); 1.68 (dd, J_1=7.7 Hz, J_2= 10.8 Hz, 1H); 2.02 (dd, J_1=7.1Hz, J_2= 10.7 Hz, 1H); 2.28 (br d, J=10.7 Hz, 1H); 2.35-2.52 (m, 2H); 2.66 (br d, J=10.6 Hz, 1H); 2.82 (dd, J_1=7.4 Hz, J_2= 13.9 Hz, 1H); 3.16 (dd, J_1=4.6 Hz, J_2= 14.0 Hz, 1H); 3.32 (s, 3H); 4.77 (s, 1H); 5.10 (d, J=10.3 Hz, 1H); 5.16 (d, J=17.3 Hz, 1H); 5.70-5.84 (m, 1H); 6.43

(d, J=7.4 Hz, 1H); 6.56 (s, 1H); 6.64 (d, J=8.0 Hz, 1H); 7.02-7.22 (m, 9H); 9.31 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 488 (M+1,100%), 334 (11%), 153 (68%). $[\alpha]_D^{20}$ = + 6.9° (ethanol, c= 1.6). The free amine (0.390 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.3 followed by precipitation with diethyl ether from dichloromethane to give 0.327 g (78% recovery) of the monohydrochloride salt as a hygroscopic light yellow powder. Calc. for $C_{30}H_{34}N_3O_2F$ HCl H_2O: C, 66.47; H, 6.88; N, 7.75; F, 3.50; Cl, 6.54. Found: C, 66.36; H, 6.74; N, 7.82; F, 3.27; Cl, 6.62.

EXAMPLE 4

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-(4-chlorophenyl)-N-methylbenzamide

4-Chloro-N-methylaniline was prepared from 4-chloroaniline, coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-chlorophenyl)-N-methylbenzamide as a light yellow powder. NMR (300 MHz, DMSO-d_6): δ 0.89 (d, J=6.2 Hz, 3H); 0.96 (d, J=6.1 Hz, 3H); 1.65 (dd, J_1=7.6 Hz, J_2=10.8 Hz, 1H); 2.01 (dd, J_1=7.6 Hz, J_2= 10.4 Hz, 1H); 2.27 (dd, J_1=1.5 Hz, J_2= 11.4 Hz, 1H); 2.35-2.52 (m, 2H); 2.65 (br d, J=10.8 Hz, 1H); 2.82 (dd, J_1=7.6 Hz, J_2= 13.5 Hz, 1H); 3.16 (dd, J_1=4.5 Hz, J_2= 14.6 Hz, 1H); 3.33 (s, 3H); 4.77 (s,1H); 5.10 (d, J=10.2 Hz, 1H); 5.16 (d, J=17.2 Hz, 1H); 5.70-5.86 (m, 1H); 6.42 (d, J= 8.1 Hz, 1H); 6.56 (s, 1H); 6.64 (d, J= 7.5 Hz, 1H); 7.04-7.25 (m, 5H); 7.13 (d, J=8.5 Hz, 2H); 7.29 (d, J=8.5 Hz, 2H); 9.31 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 504 (^{35}Cl, M+1, 86%), 350 (28%), 153 (100%). $[\alpha]_D^{20}$ = + 10.2° (ethanol, c= 1.6). The monohydrochloride salt was prepared as in Example 3 to give a hygroscopic light-yellow powder. Calc. for $C_{30}H_{34}N_3O_2Cl$ HCl 0.75H_2O: C, 65.04; H, 6.64; N, 7.58; Cl, 12.80. Found: C, 65.04; H, 6.71; N, 7.49; Cl, 12.83.

EXAMPLE 5

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-ethyl-N-phenylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)-benzyl)benzoyl chloride (Example 2, *infra*, 2.81 g crude, approximately 1.74 g. actual compound, 3.39 mmol based on 3-((αR)-α-((2S, 5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid) was dissolved in 10 mL of dichloromethane at room temperature under nitrogen. Triethylamine (0.5 mL) was added to the solution. Then N-ethylaniline (0.780 mL, 6.2 mmol) was added dropwise to the solution (exothermic), and the reaction was stirred overnight at room temperature. All volatiles were removed by evaporation under reduced pressure to provide a thick brown oil.

The crude oil was dissolved in acetonitrile (10 mL) under nitrogen at room temperature. Tetraethylammonium fluoride hydrate (1.5 g, 8.1 mmol) was added and the solution was stirred for 1 hour at room temperature. After removal of solvent, the residue was purified by chromatography on silica gel (4 cm x 15 cm) with 0.5-3% ethanol in dichloromethane to give 0.508 g (31% over 4 steps from 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid) of (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-phenylbenzamide as a white solid. NMR (300 MHz, DMSO-d_6): δ 0.89 (d, J=6.1 Hz, 3H); 0.96 (d, J=6.1 Hz, 3H); 1.07 (t, J=7.0 Hz, 3H); 1.67 (dd, J_1=7.4 Hz, J_2= 10.4 Hz, 1H); 2.02 (dd, J_1=7.4Hz, J_2= 10.6 Hz, 1H); 2.27 (dd, J_1=1.4 Hz, J_2= 10.6 Hz, 1H); 2.36-2.52 (m, 2H); 2.66 (br d, J=10.4 Hz, 1H); 2.82 (dd, J_1=7.8 Hz, J_2= 13.5 Hz, 1H); 3.16 (dd, J_1=4.0 Hz, J_2= 13.9 Hz, 1H); 3.83 (q, J=7.0 Hz, 2H); 4.75 (s, 1H); 5.09 (d, J=9.9 Hz, 1H); 5.16 (d, J=17.2 Hz, 1H); 5.70-5.84 (m, 1H); 6.41 (d, J= 7.6 Hz, 1H); 6.54 (s, 1H); 6.63 (d, J= 8.2 Hz, 1H); 7.03-7.29 (m, 10H); 9.30 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 484 (M+1,100%), 330 (57%), 153 (66%). $[\alpha]_D^{20}$= + 10.4° (ethanol, c= 1.2). The monohydrochloride salt was prepared from 0.473 g of the free amine as in Example 3 to give 0.389 g (76% recovery) of a hygroscopic white powder. Calc. for $C_{27}H_{37}N_3O_2$ HCl H_2O: C, 69.19; H, 7.49; N, 7.81; Cl, 6.59. Found: C, 69.41; H, 7.52; N, 7.73; Cl, 6.48.

EXAMPLE 6

(-)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-phenylbenzamide

This compound was obtained as a light yellow powder from aniline and 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(t-butyl-dimethylsilyloxy)benzyl)benzoyl chloride (Example 2, *infra*) using the Benzamide-Formation Method described in Example 2. NMR (200 MHz, DMSO-d_6): δ 0.99 (d ,J=5.7 Hz, 3H); 1.10 (d, J=5.8 Hz, 3H); 1.91 (dd, J_1=7.0 Hz, J_2= 10.5 Hz, 1H); 2.14 (dd, J_1=6.0Hz, J_2= 10.4 Hz, 1H); 2.51-2.81(m, 4H); 2.88 (dd, J_1=6.8 Hz, J_2= 13.9 Hz, 1H); 3.18 (dd, J_1=5.4 Hz, J_2= 13.8 Hz, 1H); 5.06 (d, J=15.6 Hz, 1H); 5.14 (s, 1H); 5.19 (d, J=18.1 Hz, 1H); 5.75 (m, 1H); 6.73 (m, 3H); 7.10 (d, J=7.8 Hz, 1H); 7.17 (d, J= 8.0 Hz, 1H); 7.30-7.59 (m, 3H); 7.65 (d, J= 7.6 Hz, 1H); 7.71-7.83 (m, 3H); 7.93 (s, 1H); 9.37 (s, 1H); 10.21 (s, 1H). Mass spectrum (CI-CH_4) m/e: 456 (M+1,100%), 302 (41%), 153 (77%). $[\alpha]_D^{20}$= -4.44° (ethanol, c= 1.4). The monohydrochloride salt was prepared as in Example 2 to give a hygroscopic light yellow powder. Calc. for $C_{29}H_{33}N_3O_2$ HCl 0.75 H_2O: C, 68.90 H, 7.08; N, 8.31; Cl, 7.01. Found: C, 69.00; H, 7.06; N, 8.32; Cl, 6.95.

EXAMPLE 7

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide

1-((3-Fluoro-N-methylaniline was prepared from 3-fluoroaniline using a modified reductive amination. First, 1-hydroxymethylbenzotriazole was prepared by adding 37% aqueous formaldehyde to benzotriazole at 40 °C in a 1:1 ratio and cooling to room temperature to precipitate the product. After filtration the hydroxymethylbenzotriazole (125 g) was heated to reflux in toluene with 3-fluoroaniline (92.2 g). Water was removed azeotropically using a Dean-Stark trap. After three hours, the mixture was cooled to room temperature, then refrigerated for several hours to complete precipitation. The white crystalline solid was collected by filtration, yielding 174.2 g (86.6%) of 1-(3-fluoroanilino)methyl)-1H-benzotriazole.

1-((3-Fluoroanilino)methyl)-1H-benzotriazole (173.9 g) was slurried in dry tetrahydrofuran. Sodium borohydride (32.5 g) was added portionwise to the mixture at room temperature. After addition was complete, the mixture was heated at reflux for 4 hours. The solution was cooled and poured slowly into 400 mL of 5 M hydrochloric acid with ice and stirred for 1 hour at room temperature. The solution pH was adjusted to 9-10 using 10 M sodium hydroxide solution. The product was extracted using diethyl ether. The ether extracts were washed successively with 1 M sodium hydroxide solution, saturated sodium chloride solution, and water. The organic phase was dried over sodium sulfate and evaporated under reduced pressure to yield 87.5 g (97%) of 3-fluoro-N-methylaniline as a colorless oil. [NMR (200 MHz, DMSO-d_6): δ 2.76 (s, 3H); 3.41 (br s, 1H); 6.59-6.92 (m, 3H); 7.27 (q, J=8.0Hz, 1H)].

3-Carboxybenzaldehyde (Alfrebro Inc., Monroe, Ohio; 2.0 g.) was slurried in thionyl chloride (6 mL). A reflux condenser fitted with a calcium chloride drying tube was placed on the flask. The reaction was placed in an oil bath and heated at a bath temperature maintained below 100 °C. The mixture was allowed to reflux until a clear solution was obtained and for 5-10 additional minutes before cooling to room temperature. The solution was diluted with anhydrous toluene, and all volatiles were removed under vacuum.

The crude acid chloride was dissolved in dichloromethane and cooled in an ice/water bath. Triethylamine (6 mL) was added dropwise via an addition funnel, followed by N-methyl-3-fluoroaniline (1.83 g) in dichloromethane. The cloudy solution was allowed to warm to room temperature over 1 hour. Water was added and the product was extracted with dichloromethane. The organic layer was washed with water and saturated sodium chloride solution and dried over sodium sulfate, and the solvent was removed under vacuum. N-(3-Fluorophenyl)-3-formyl-N-methylbenzamide (3.20 g) was obtained as a light golden oil (93% unchromatographed yield). [NMR (300 MHz, DMSO-d_6): δ 3.38 (s, 3H); 6.94-7.02 (m, 2H); 7.18-7.29 (m, 2H); 7.46 (t, J= 7.7 Hz, 1H) 7.55 (d, J=7.6 Hz, 1H); 7.81 (m, 2H); 9.90 (s, 1H)].

A 12 L, 3-necked round bottom flask was charged with *trans*-2,5-dimethylpiperazine (767 g, 6.72 mol), which had been recrystallized from toluene to mp=115-119 °C, and 600 mL of water. The flask was cooled in an ice bath and a solution of methanesulfonic acid (1290 g, 13.4 mol) in 600 mL of water was added slowly with stirring and cooling to maintain the temperature below 40

°C. The solution was cooled to 20 °C and 800 mL of ethanol was added. A 500 mL addition funnel was filled with 60% aqueous potassium acetate from a 2 L reservoir of the solution, and potassium acetate was added to the reaction flask to adjust the pH to 4.0. A second addition funnel was charged with a solution of ethyl chloroformate (642 mL, 6.71 mol) in 360 mL of tetrahydrofuran. The ethyl chloroformate and potassium acetate solutions were simultaneously added dropwise with adjustment of rate to maintain the reaction solution at pH 4.0 $\pm$0.1, with cooling as necessary to maintain temperature at 25 °C. After addition of the ethyl chloroformate was complete, the reaction was stirred for 1 hour with continued addition of potassium acetate solution to maintain a pH of 4.0. The organic solvents were removed by distillation under vacuum. The remaining aqueous solution was washed with 1500 mL of ethyl acetate to remove any bis-carbamate impurity. The ethyl acetate wash was extracted with two 500 mL portions of 1 M hydrochloric acid to recover desired product. The acid extracts were combined with the original aqueous solution and the pH was adjusted to 11 by addition of 10 M sodium hydroxide, with cooling to maintain temperature below 40 °C. The aqueous solution was extracted with two 1500 mL portions of ethyl acetate, the combined extracts were dried over magnesium sulfate, and the solvent was removed to give 927 g (74%) ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate as a yellow oil.

A mixture of ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate (643 g, 3.45 mol), allyl bromide (328 mL, 3.80 mol), and sodium carbonate (440 g, 4.15 mol) in 2500 mL of acetonitrile was heated at reflux for 1.5 hours. The reaction was cooled to room temperature, filtered, and the solvent removed under vacuum. The residue was dissolved in 4000 mL of dichloromethane and washed with two 500 mL portions of 1 M sodium hydroxide. The dichloromethane solution was dried over magnesium sulfate and the solvent was removed to give 630 g (81%) of ethyl *trans*-4-allyl-2,5-dimethyl-1-piperazinecarboxylate as an oil.

Ethyl *trans*-4-allyl-2,5-dimethyl-1-piperazinecarboxylate (630 g, 2.78 mol) was added to a solution of 87% potassium hydroxide pellets (2970 g, 46 mol) in 4300 mL of 95% ethanol and heated at reflux for 1.5 hours. Carbon dioxide evolution was observed for the first 0.5 - 1 hour of heating. The reaction was cooled below reflux temperature and 2000 mL of toluene was carefully added. Ethanol was removed by azeotropic distillation at 105 °C, while adding an additional 4000 mL of toluene to the reaction flask during the course of the distillation. After collection of 9000 mL of distillate, the reaction was cooled to 100 °C and 1000 mL of toluene was carefully added. The

solution was slowly cooled to 5 °C and maintained at 5 °C for 30 minutes. The solution was filtered, and the filter cake was washed with an additional 1500 mL of toluene. The filtrate was washed with 1000 mL of water, dried over magnesium sulfate, and the solvent was removed to give 296 g (69%) of *trans*-1-allyl-2,5-dimethylpiperazine as a dark liquid. NMR (300 MHz, DMSO-d_6): δ 0.87 (d, J=6.3 Hz, 3H); 0.92 (d, J=6.3 Hz, 3H); 1.63 (t, J=11 Hz, 1H); 2.05 (m, 1H); 2.30 (t, J=11 Hz, 1H); 2.6-2.8 (m, 4H); 3.33 (dd, J_1= 5 Hz, J_2= 14 Hz, 1H); 5.09 (d, J=8.7 Hz, 1H); 5.13 (d, J=14 Hz, 1H) 5.8 (m, 1H).

Di-*p*-toluoyl-D-tartaric acid (Schweizerhall, Inc., South Plainfield, New Jersey) (1.25 Kg, 3.2 mol) was dissolved in hot (~60 °C) 95% ethanol (16 L) and racemic *trans*-1-allyl-2,5-dimethylpiperazine (500 g, 3.2 mol) was added in several portions (caution: exothermic). The hot solution was seeded with crystals of the diastereoisomerically pure salt (obtained from a previous small-scale resolution) and cooled to room temperature over 2-3 hours. The solution was slowly stirred for 2\ days at room temperature. The resulting salt was collected by filtration, washed twice with 95% ethanol, and dried under vacuum to give 826.5 g of a white solid (47%). The process was repeated with a second batch of the di-*p*-toluoyl-D-tartaric acid and racemic *trans*-1-allyl-2,5-dimethylpiperazine to give 869 g (50%).

The total of 1695 g of salt was divided into three batches and each batch was recrystallized twice in the following fashion. The salt was dissolved in refluxing 95% ethanol (~2.7 L/100 g of salt), and approximately half of the ethanol was removed by distillation. (Note: vigorous stirring was necessary during distillation to prevent crystallization on the vessel wall.) The hot solution was seeded with crystals of the pure diastereomeric salt, cooled to room temperature, and stirred slowly for 2 days before collecting the salt by filtration. (Note: a subsequent experiment suggested that crystallization time can be reduced from 2 days to 8 hours.) The total amount recovered was 1151 g. The salt was dissolved in 3 L of 2 M aqueous sodium hydroxide, and the aqueous solution was extracted with four 1 L portions of dichloromethane. The organic extracts were combined, dried over sodium sulfate, and solvent removed by rotary evaporation (temperature < 20 °C) to give 293 g (29% based on racemic weight) of (2R,5S)-1-allyl-2,5-dimethylpiperazine as a clear oil. $[\alpha]_D^{20}$ = -55.1° (abs. ethanol, c=1.2). The trifluoroacetamide of the product was prepared with trifluoroacetic anhydride and analyzed by chiral capillary gas chromatography (Chiraldex B-PH column, 20 m x 0.32 mm, Advanced Separation Technologies Inc., Whippany, NJ, 120 °C) indicating an

enantiopurity of >99% ee (retention time of desired enantiomer, 11.7 min; other enantiomer, 10.7 min).

(2R,5S)-1-allyl-2,5-dimethylpiperazine (6.13 g), benzotriazole (4.79 g), and N-(3-fluorophenyl)-3-formyl-N-methylbenzamide (10.23 g) were mixed in dry toluene with one drop of triethylamine. The mixture was placed in an oil bath maintained at 140 °C (bath temperature). The flask was attached to a Dean-Stark trap to allow the azeotropic removal of water, under a stream of nitrogen. The mixture was heated at reflux for 2-3 hours and most of the toluene was removed under reduced pressure. The crude adduct may be isolated by crystallization at this stage to give 3-(((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(1H-benzotriazol-1-yl)methyl)-N-(3-fluorophenyl)-N-methylbenzamide as a mixture of epimers, but due to the water-sensitive nature of the adduct, it is generally easier to use the crude material for subsequent reactions. (The reaction mixture in toluene is usually satisfactory for the next step.)

A solution of 3-bromophenol (500 g, 2.89 mol), tert-butylchlorodimethylsilane (436 g, 2.89 mol), and imidazole (500 g, 7.22 mol) in 500 mL of dimethylformamide was stirred overnight at room temperature. The reaction solution was poured into 3000 mL of water and extracted with two 2000 mL portions of diethyl ether. The combined ether extracts were dried over sodium sulfate and the solvent removed to give 846 g of 3-(bromophenoxy)-tert-butyldimethylsilane as a pale yellow liquid. NMR (300 MHz, $CDCl_3$): δ 0.2 (s, 6H); 1.0 (s, 9H); 6.75 (m, 1H); 7.0 (br s, 1H); 7.1 (m, 2H).

3-(Bromophenoxy)-tert-butyldimethylsilane (17.12 g) was dissolved in dry tetrahydrofuran (150 mL), and cooled to -78 °C under nitrogen. n-Butyllithium in hexanes (23.88 mL of a 2.5M solution) was added slowly via syringe to the solution. While stirring for 40 minutes at -78 °C, the solution became white and somewhat thick. The solution was transferred via a double-ended needle to a flask containing magnesium bromide etherate (16.5 g) in tetrahydrofuran (150 mL) and stirred for 1 hour at room temperature. The crude benzotriazole adduct from above containing primarily 3-(((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(1H-benzotriazol-1-yl)methyl)-N-(3-fluorophenyl)-N-methylbenzamide was dissolved in tetrahydrofuran and added to the arylmagnesium bromide reagent just prepared. The solution warmed slightly during the addition and became a cloudy yellow-brown color. After stirring at room temperature for 2 hours, 0.5 M

aqueous hydrochloric acid was added cautiously until the solution reached pH=6. The product was extracted with 250 mL of ethyl acetate and the solvent was removed under vacuum.

The tert-butyldimethylsilyl protecting group was removed by dissolving the residue in 175 mL of tetrahydrofuran and adding 85 mL of 3N aqueous HCl at room temperature. The solution warmed upon acid addition. The mixture was stirred for 40 minutes at room temperature. Diethyl ether was added, and the acidic aqueous layer was separated. The aqueous layer was washed a second time with diethyl ether and adjusted to pH=8-9 using aqueous sodium hydroxide solution. The product was extracted using ethyl acetate. The ethyl acetate portions were combined, and washed with dilute sodium hydroxide solution to remove any remaining benzotriazole. The organic layer was then washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated under reduced pressure. The product (10.85 g, 56%) was recovered as a mixture of two diastereomers in a 91:9 ratio favoring the desired diastereomer, as determined by HPLC analysis. HPLC was performed on a μ-Bondapak C-18 column (125Å, 3.9 x 300 mm, Waters Chromatography Division, Millipore Corporation, Milford, MA) using 60% methanol and 40% 0.1 M aqueous ammonium acetate at a flow rate of 1 mL/min. The diastereomeric mixture was recrystallized from ethyl acetate/hexane to give (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide as a white crystalline solid (mp 144-145 °C) in 99% isomeric purity (as determined by HPLC). NMR (200 MHz, DMSO-d6): δ 0.84 (d, J=6.0 Hz, 3H); 0.97 (d, J=5.9 Hz, 3H); 1.69 (dd, J_1=7.7 Hz, J_2= 10.7 Hz, 1H); 2.01 (dd, J_1=7.4 Hz, J_2=10.7 Hz, 1H); 2.28 (br d, J=8.3 Hz, 1H); 2.40-2.52 (m, 2H); 2.67 (br d, J=10.5 Hz, 1H); 2.82 (dd, J_1=7.6 Hz, J_2=13.2 Hz, 1H); 3.17 (br d, J= 14.0 Hz, 1H); 3.34 (s, 3H); 4.80 (s, 1H); 5.10 (d, J=10.1 Hz, 1H); 5.17 (d, J=17.3 Hz, 1H); 5.70-5.84 (m, 1H); 6.42 (d, J=7.1 Hz, 1H); 6.56 (s, 1H); 6.65 (d, J=8.3 Hz, 1H); 6.90-7.32 (m, 9H); 9.31 (s, 1H). Mass spectrum (CI-CH_4) m/e: 488 (m+1, 100%), 334 (39%), 153 (87%). $[\alpha]_D^{20}$ = + 4.9° (abs. ethanol, c= 1.2).

The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.7 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic off-white powder. Calc. for $C_{30}H_{34}N_3O_2F$ HCl 1.25 H_2O: C, 65.92; H, 6.92; N, 7.69; Cl, 6.49. Found: C, 66.07; H, 6.95; N, 7.53; Cl, 6.54.

EXAMPLE 8

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-methyl-N-(2,4,6-trichlorophenyl)benzamide

N-Methyl-2,4,6-trichloroaniline [NMR (200 MHz, $CDCl_3$): δ 2.82 (s, 3H); 5.11 (s, 1H); 7.46 (s, 2H)] was prepared from 2,4,6-trichloroaniline, coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-(2,4,6-trichlorophenyl)benzamide as an off-white powder. NMR (200 MHz, DMSO-d_6): δ 0.90 (d, J=6.1 Hz, 3H); 0.98 (d, J=6.0 Hz, 3H); 1.65 (dd, J_1=7.4 Hz, J_2= 10.6 Hz, 1H); 2.03 (dd, J_1=7.5 Hz, J_2= 10.2 Hz, 1H); 2.35 (d, J=11.7 Hz, 1H); 2.38-2.51 (m, 2H); 2.65 (br d, J=10.6 Hz, 1H); 2.80 (dd, J_1=7.0 Hz, J_2= 13.3 Hz, 1H); 3.12 (m, 1H); 3.18 (s, 3H); 4.80 (s, 1H); 5.11 (d, J=11.0 Hz, 1H); 5.18 (d, J=16.8 Hz, 1H); 5.66-5.87 (m, 1H); 6.48 (d, J=8.4 Hz, 1H); 6.56 (s, 1H); 6.64 (d, J= 8.6 Hz, 1H); .7.16 (t, J=8.0, 1H);7.22-7.28 (m, 3H); 7.38 (s, 1H); 7.69 (d, J= 2.2 Hz, 1H); 7.72 (d, J= 2.2 Hz, 1H); 9.31 (s, 1H). Mass spectrum (CI-CH_4) m/e: 572 (M+1, 14%), 153 (100%).

EXAMPLE 9

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-methyl-N-(2-(trifluoromethyl)phenyl)benzamide

N-Methyl-2-(trifluoromethyl)aniline [NMR (200 MHz, DMSO-d_6): δ 2.75 (s, 3H); 3.40 (s, 1H); 6.70 (t, J= 8.0 Hz, 1H); 6.94-7.16 (br. m, 2H); 7.38 (d, J=7.3 Hz, 1H)] was prepared from 2-(trifluoromethyl)aniline, coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-(2-(trifluoromethyl)phenyl)benzamide as a yellow powder. NMR (200 MHz, DMSO-d_6): δ 0.90 (d, J=6.0 Hz, 3H); 0.97 (d, J=6.0 Hz, 3H); 1.64 (m, 1H); 2.05 (m, 1H); 2.27 (br d, J=10.5 Hz,1H); 2.40-2.84 (m, 4H); 3.18 (br d, J= 13.5 Hz, 1H); 3.29 (s, 3H); 4.79 (s, 1H); 5.11 (d, J=10.2 Hz, 1H); 5.18 (d, J=17.0 Hz, 1H); 5.70-5.82 (m, 1H); 6.42 (d, J=7.6 Hz, 1H); 6.65

(d, J=7.7 Hz, 1H); 6.67 (s, 1H); 7.04-7.83 (m, 9H); 9.32 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 538 (M+1, 82%), 384 (13%), 153 (100%).

EXAMPLE 10

(+)-3-((αS)-α-((2S, 5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-methyl-N-phenylbenzamide

3-((αS)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-bromobenzyl)phenol (2.30 g, 5.5 mmol, Example 2, *infra*) was treated with tert-butylchlorodimethylsilane (1.67 g, 11 mmol) and imidazole (0.94 g, 13.8 mmol) in 30 mL of dimethylformamide at room temperature under nitrogen overnight. The reaction mixture was poured into ice-water and extracted with diethyl ether. The ethereal layers were washed with water and brine, dried over sodium sulfate, and concentrated to dryness. The residue was purified by chromatography on silica gel with hexane:ethyl acetate (0-50%) to give 2.36 g of the silyl ether as a yellow oil.

The silyl ether (2.25 g, 4.2 mmol) was dissolved in 80 mL of dry tetrahydrofuran, dried further over molecular sieves, then transferred to a reaction flask under nitrogen and cooled to -78 °C. n-Butyllithium (2.6 mL of a 1.6M solution in hexane) was added, while stirring under nitrogen, at a rate to keep the temperature below -70 °C. Stirring was continued at -78 °C for 1 hour. Carbon dioxide was bubbled through the reaction mixture for 2-3 minutes. The mixture was warmed to room temperature with continual stirring to maintain steady degassing of dissolved carbon dioxide. The solvent was evaporated, the residue was redissolved in toluene, and the solvent was again removed under vacuum to eliminate all n-bromobutane. The residue was dissolved in dichloromethane (50 mL), thionyl chloride (0.46 mL, 6.3 mmol) was added, and the mixture was stirred at room temperature for 40 minutes. Triethylamine (2.3 mL, 16.8 mmol) and N-methylaniline (0.5 mL, 4.6 mmol) were added, and stirring was continued at room temperature overnight. The reaction mixture was washed with water, dried over sodium sulfate, and the solvent was removed under vacuum to give 2.68 g of a brown oil. The crude product was dissolved in acetonitrile and treated with 1.2 g (6.3 mmol) of tetraethylammonium fluoride dihydrate at room temperature for 10 minutes. The solvent was evaporated and the residue was purified by chromatography on silica gel with dichloromethane:ethanol (0-3.5%) to give 0.92 g of (+)-3-((αS)-

α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-phenylbenzamide as a light beige solid. NMR (DMSO-d_6, 200 MHz) δ: 0.9 (d, J=6 Hz, 3H); 0.95 (d, J=6 Hz, 3H); 1.7 (dd, J_1= 6 Hz, J_2= 8 Hz, 1H); 2.0 (dd, J_1=7 Hz, J_2=10 Hz, 1H); 2.1 (m, 1H); 2.4-2.7 (m, 3H); 2.85 (dd, J_1= 7 Hz, J_2=14 Hz, 1H); 3.15 (dd, J_1=7 Hz, J_2=15 Hz, 1H); 3.4 (s, 3H); 4.7 (s, 1H); 5.1 (d, J=10 Hz, 1H); 5.2 (d, J=17 Hz, 1H); 5.8 (m, 1H); 6.6 (m, 2H); 6.8 (s, 1H); 7.0 (t, J=8 Hz, 1H); 7.1-7.3 (m, 9H); 9.4 (s, 1H). $[\alpha]_D^{20}$ = +4° (abs ethanol, c=2.7). The product was dissolved in absolute ethanol and titrated to pH 3 with ethanolic hydrogen chloride. The solution was concentrated and diethyl ether was added to precipitate the monohydrochloride salt which was dried under vacuum to give 0.617 g of a light beige powder. Calc. for $C_{30}H_{35}N_3O_2$ HCl 0.70 H_2O: C, 69.47; H, 7.27; N, 8.10; Cl, 6.84. Found: C, 69.76; H, 7.27; N, 7.74; Cl, 6.60.

EXAMPLE 11

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-phenyl-N-propylbenzamide

N-Propylaniline was prepared from aniline and propionic anhydride, coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-phenyl-N-propylbenzamide as a light yellow solid. NMR (200 MHz, DMSO-d_6): δ 0.87 (t, J=7.4 Hz, 3H); 0.91 (d, J=5.9 Hz, 3H); 0.98 (d, J=6.0 Hz, 3H);1.51 (m, 2H); 1.69 (dd, J_1=7.2 Hz, J_2=10.9 Hz, 1H); 2.06 (dd, J_1=7.0 Hz, J_2=10.5 Hz, 1H); 2.30 (d, J=10.3Hz, 1H); 2.39-2.54 (m, 2H); 2.65 (br d, J=10.3 Hz, 1H); 2.85 (dd, J_1=7.4 Hz, J_2=14.5 Hz, 1H); 3.16 (dd, J_1=5.1 Hz, J_2=14.2 Hz, 1H); 3.79 (t, J=7.6 Hz, 2H); 4.77 (s,1H); 5.12 (d, J=10.2 Hz, 1H); 5.18 (d, J=16.0 Hz, 1H); 5.71-5.84 (m, 1H); 6.43 (d, J=7.6 Hz, 1H); 6.57 (s, 1H); 6.64 (d, J=8.0 Hz, 1H); 7.02-7.33 (m, 10H); 9.32 (s, 1H). Mass spectrum (CI-CH_4) m/e: 498 (M+1,100%), 344 (23%), 153 (80%). $[\alpha]_D^{20}$ = + 8.9° (ethanol, c= 1.1). The free amine (0.585 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give 0.479 g of the monohydrochloride salt as a hygroscopic off-white powder. Calc. for $C_{32}H_{39}N_3O_2$ HCl 0.75 H_2O: C, 70.18; H, 7.64; N, 7.67; Cl, 6.47. Found: C, 70.16; H, 7.73; N, 7.59; Cl, 6.51.

EXAMPLE 12

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide

4-Fluoro-N-ethylaniline [NMR (200 MHz, DMSO-d_6): δ 1.25 (t, J=7.1 Hz, 3H); 3.12 (q, J=7.1 Hz, 2H); 3.24 (br s, 1H); 6.57 (dd, J_1=4.5 Hz, J_2=9.0 Hz, 2H); 6.90 (t, J=8.9 Hz, 2H)] was prepared from 4-fluoroaniline and acetic anhydride by the methods described in Example 3. The aniline was used to form N-(4-fluorophenyl)-3-formyl-N-ethylbenzamide [NMR (200 MHz, DMSO-d_6): δ 1.11 (t, J=7.0 Hz, 3H); 3.88 (q, J=7.0 Hz , 2H); 7.10 (t, J=8.6 Hz, 2H); 7.21-7.35 (m, 2H); 7.46 (q, J=7.4 Hz, 1H); 7.56 (d, J=7.2 Hz, 1H); 7.83 (m, 2H); 9.93 (s, 1H)] by the methods described in Example 7. (+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide was obtained as a white crystalline solid from N-(4-fluorophenyl)-3-formyl-N-ethylbenzamide via crude 3-(((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(1H-benzotriazol-1-yl)methyl)-N-ethyl-N-(4-fluorophenyl)benzamide using the procedures described in Example 7. The final recrystallization was performed in acetonitrile. NMR (200 MHz, DMSO-d_6): δ 0.91 (d, J=6.1 Hz, 3H); 0.98 (d, J=6.0 Hz, 3H); 1.08 (t, J=7.0 Hz, 3H); 1.71 (dd, J_1=7.0 Hz, J_2= 11.3 Hz, 1H); 2.05 (dd, J_1=7.2Hz, J_2= 10.8 Hz, 1H); 2.31 (d, J=11.4 Hz, 1H) 2.36-2.57 (m, 2H); 2.69 (dd, J_1=2.2 Hz, J_2= 10.7 Hz, 1H); 2.85 (dd, J_1=7.0 Hz, J_2=13.9 Hz, 1H); 3.18 (dd, J_1=5.3 Hz, J_2= 13.9 Hz, 1H); 3.84 (q, J=7.0 Hz, 2H); 4.78 (s, 1H); 5.11 (d, J=10.0 Hz, 1H); 5.18 (d, J=16.4 Hz, 1H); 5.65-5.88 (m, 1H); 6.46 (d, J= 7.4 Hz, 1H); 6.58 (s, 1H); 6.65 (d, J= 8.1 Hz, 1H); 7.01-7.27 (m, 9H); 9.33 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 502 (M+1, 90%), 348 (15%), 153 (100%). $[\alpha]_D^{20}$ = + 6.30° (abs. ethanol, c= 1.1).

The free amine (0.313 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.95 followed by precipitation with diethyl ether from dichloromethane to give 0.263 g of the monohydrochloride salt as a hygroscopic white powder. Calc. for $C_{31}H_{36}N_3O_2F$ HCl H_2O: C, 66.95; H, 7.07; N, 7.56; Cl, 6.38. Found: C, 66.97; H, 7.10; N, 7.47; Cl, 6.41.

EXAMPLE 13

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-methoxyphenyl)-N-methylbenzamide

4-Methoxy-N-methylaniline was coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-methoxyphenyl)-N-methylbenzamide as a light purple powder. NMR (200 MHz, DMSO-d_6): δ 0.89 (d, J=6.0 Hz, 3H); 0.96 (d, J=6.1 Hz, 3H); 1.66 (dd, J_1=6.5 Hz, J_2=11.0 Hz, 1H); 2.00 (dd, J_1=7.1 Hz, J_2=10.4 Hz, 1H); 2.27 (br d, J=11.4 Hz, 1H); 2.36-2.54 (m, 2H); 2.64 (d, J=11.6 Hz, 1H); 2.82 (dd, J_1=6.9 Hz, J_2=13.6 Hz, 1H); 3.18 (dd, J_1=5.4 Hz, J_2=12.8 Hz, 1H); 3.30 (s, 3H); 3.68 (s, 3H); 4.76 (s, 1H); 5.11 (d, J=10.6 Hz, 1H); 5.18 (d, J=17.1 Hz, 1H); 5.66-5.88 (m, 1H); 6.42 (d, J=7.1 Hz, 1H); 6.58 (s, 1H); 6.63 (d, J=7.4 Hz, 1H); 6.78 (d, J= 8.8 Hz, 2H); 6.97-7.24 (m, 7H); 9.34 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 500 (M+1, 79%), 346 (49%), 153 (100%). $[\alpha]_D^{20}$ = + 9.6° (abs. ethanol, c= 1.0). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic light purple powder. Calc. for $C_{31}H_{37}N_3O_3$ HCl H_2O: C, 67.19; H, 7.28; N, 7.58; Cl, 6.40. Found: C, 67.01; H, 7.30; N, 7.53; Cl, 6.42.

EXAMPLE 14

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-methylbenzamide

2-Fluoro-N-methylaniline [NMR (200 MHz, DMSO-d_6): δ 2.89 (s, 3H); 3.87 (br s, 1H); 6.59-6.78 (m, 2H); 6.91-7.10 (m, 2H)] was prepared from 2-fluoroaniline, coupled with 3-((aR)-a-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give 3-((aR)-a-((2S,5R)-4-allyl-

2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-methylbenzamide as an off-white powder. NMR (200 MHz, DMSO-d_6): δ 0.92 (d, J=6.1 Hz, 3H); 0.99 (d, J=6.1 Hz, 3H); 1.69 (dd, J_1=6.7 Hz, J_2=10.8 Hz, 1H); 2.05 (dd, J_1=7.6 Hz, J_2=11.1 Hz, 1H); 2.30 (br d, J=11.5 Hz, 1H); 2.41-2.52 (m, 2H); 2.68 (br d, J=10.4 Hz, 1H); 2.83 (dd, J_1=7.2 Hz, J_2=13.8 Hz, 1H); 3.20 (dd, J_1=6.1 Hz, J_2=14.2 Hz, 1H); 3.30 (s, 3H); 4.82 (s, 1H); 5.12 (d, J=9.7 Hz, 1H); 5.18 (d, J=15.8 Hz, 1H); 5.72-5.86 (m, 1H); 6.45 (d, J=7.4 Hz, 1H); 6.56 (s, 1H); 6.66 (d, J=8.0 Hz, 1H); 7.05-7.38 (m, 9H); 9.33 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 488 (M+1, 100%), 334 (45%), 153 (86%). $[\alpha]_D^{20}$ = + 2.02° (abs. ethanol, c= 1.1). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic beige powder. Calc. for $C_{30}H_{34}N_3O_2F$ HCl 0.75 H_2O: C, 67.03; H, 6.84; N, 7.82; Cl, 6.59. Found: C, 67.05; H, 6.86; N, 7.77; Cl, 6.67.

EXAMPLE 15

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-allyl-N-phenylbenzamide

N-Allylaniline [NMR (200 MHz, DMSO-d_6): δ 3.68 (t, J=5.2 Hz, 2H); 5.10 (d, J=10.2 Hz, 1H); 5.23 (d, J=17.2 Hz, 1H);5.78 (br s, 1H); 5.75-5.97 (m, 1H); 6.52 (t, J=7.3 Hz, 2H); 6.56 (d, J=7.8 Hz, 2H); 7.06 (t, J=7.3 Hz, 2H)] was prepared from aniline and allyl bromide via trifluoroacetanilide using the general method described by Hodge (Harland, P.A.; Hodge, P; Maughan, W.; Wildsmith, E. *Synthesis*, 1984, 941).

N-Allylaniline was coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-allyl-N-phenylbenzamide as an off-white powder. NMR (200 MHz, DMSO-d_6): δ 0.91 (d, J=6.3 Hz, 3H); 0.97 (d, J=5.8 Hz, 3H); 1.67 (dd, J_1=6.7 Hz, J_2=10.6 Hz, 1H); 2.03 (dd, J_1=7.0 Hz, J_2=10.3 Hz, 1H); 2.29 (d, J=11.9 Hz, 1H); 2.39-2.53 (m, 2H); 2.67 (br d, J=11.2 Hz, 1H); 2.83 (dd, J_1=6.8 Hz, J_2=14.4 Hz, 1H); 3.17 (dd, J_1=5.2 Hz, J_2=14.0 Hz, 1H); 4.45 (d, J=5.5 Hz, 2H); 4.78 (s,1H); 5.11 (d, J=7.4 Hz, 1H); 5.12 (d, J=8.5 Hz, 1H); 5.17 (d, J=11.9 Hz, 1H); 5.18

(d, J=15.3 Hz, 1H); 5.71-5.98 (m, 2H); 6.42 (d, J=7.6 Hz, 1H); 6.56 (s, 1H); 6.65 (d, J=7.8 Hz, 1H); 7.02-7.33 (m, 10H); 9.33 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 496 (M+1, 45%), 342 (22%), 153 (100%). $[\alpha]_D^{20}$= + 6.0° (abs. ethanol, c= 1.1). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.8 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic off-white powder. Calc. for $C_{32}H_{37}N_3O_2$ HCl H_2O: C, 69.86; H, 7.33; N, 7.64; Cl, 6.44. Found: C, 69.94; H, 7.24; N, 7.62; Cl, 6.52.

EXAMPLE 16

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(cyclopropyl)methyl-N-phenylbenzamide

N-(Cyclopropylmethyl)aniline [NMR (200 MHz, DMSO-d_6): δ 0.21 (m, 2H); 0.51 (m, 2H); 1.01 (m, 1H); 3.63 (d, J=7.3 Hz, 1H); 3.80 (br s, 1H); 5.78 (br s, 1H); 7.18 (t, J=7.2 Hz, 1H); 7.25 (d, J=7.8 Hz, 2H); 7.42 (t, J=7.3 Hz, 2H)] was prepared from aniline and (bromomethyl)cyclopropane via trifluoroacetanilide using the general method described by Hodge (Harland, P.A.; Hodge, P; Maughan, W.; Wildsmith, E. *Synthesis*, 1984, 941.).

N-(Cyclopropyl)methylaniline was coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(cyclopropyl)methyl-N-phenylbenzamide as an off-white powder. NMR (200 MHz, DMSO-d_6): δ 0.09 (m, 2H); 0.39 (m, 2H); 0.92 (d, J=6.3 Hz,3H); 0.96 (d, J=6.2 Hz, 3H); 1.28 (m, 1H); 1.69 (dd, J_1=7.4 Hz, J_2=11.5 Hz, 1H); 2.04 (dd, J_1=6.6 Hz, J_2=11.0 Hz, 1H); 2.30 (br d, J=12.1 Hz, 1H); 2.40-2.54 (m, 2H); 2.67 (br d, J=9.8 Hz, 1H); 2.85 (dd, J_1=7.4 Hz, J_2=13.7 Hz, 1H); 3.16 (dd, J_1=4.5 Hz, J_2=14.7 Hz, 1H); 3.72 (d, J=7.0 Hz, 2H); 4.77 (s, 1H); 5.12 (d, J=10.0 Hz, 1H); 5.18 (d, J=15.6 Hz, 1H); 5.70-5.85 (m, 1H); 6.44 (d, J=7.3 Hz, 1H); 6.57 (s, 1H); 6.65 (d, J=8.0 Hz, 1H); 7.02-7.33 (m, 10H); 9.33 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 510 (M+1, 61%), 356 (42%), 153 (100%). $[\alpha]_D^{20}$= + 8.9° (abs. ethanol, c= 1.1). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.75 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a

hygroscopic off-white powder. Calc. for $C_{33}H_{39}N_3O_2$ HCl 1.25 H_2O: C, 69.70; H, 7.53; N, 7.39; Cl, 6.23. Found: C, 69.82; H, 7.52; N, 7.36; Cl, 6.28.

EXAMPLE 17

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-isopropyl-N-phenylbenzamide

N-isopropylaniline [NMR (200 MHz, DMSO-d_6): δ 1.13 (d, J=6.3 Hz, 6H); 3.58 (m, 1H); 5.30 (d, J=8.0 Hz, 1H); 6.49 (t, J=7.2 Hz, 1H); 6.55 (d, J=7.8 Hz, 2H); 7.06 (t, J=7.6 Hz, 2H)] was prepared from aniline and acetone via reductive amination using the general method described by Schellenberg (Schellenberg, K. A. *J.Org.Chem.* **1963**, *28*, 3259).

N-isopropylaniline was then coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)-benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-isopropyl-N-phenylbenzamide as an off-white solid. NMR (200 MHz, DMSO-d_6): δ 0.92 (d, J=6.1 Hz, 3H); 0.99 (d, J=5.9 Hz, 3H); 1.11 (d, J=6.9 Hz, 6H); 1.70 (dd, J_1=7.2 Hz, J_2=11.1 Hz, 1H); 2.07 (dd, J_1=7.6 Hz, J_2=10.6 Hz, 1H); 2.33 (br d, J=9.9 Hz,1H); 2.42-2.54 (m, 2H); 2.68 (br d, J=10.4 Hz, 1H); 2.85 (dd, J_1=6.5 Hz, J_2=13.9 Hz, 1H); 3.16 (dd, J_1=4.9 Hz, J_2=14.1 Hz, 1H); 4.75 (s, 1H); 4.85 (m, 1H); 5.10 (d, J=10.2 Hz, 1H); 5.18 (d, J=16.8 Hz, 1H); 5.70-5.84 (m, 1H); 6.50 (d, J=7.1 Hz, 1H); 6.59 (s, 1H); 6.65 (d, J=8.2 Hz, 1H); 7.03-7.32 (m, 10H); 9.33 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 498 (M+1, 100%), 344 (43%), 153 (76%). $[\alpha]_D^{20}$ = + 6.4° (abs. ethanol, c= 1.4). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic off-white powder. Calc. for $C_{32}H_{39}N_3O_2$ HCl 0.5 H_2O: C, 70.76; H, 7.61; N, 7.74; Cl, 6.53. Found: C, 71.01; H, 7.83; N, 7.49; Cl, 6.41.

EXAMPLE 18

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-cyclopropyl-N-phenylbenzamide

N-Cyclopropylaniline was prepared via the Barton approach for arylation of amines (Barton, D. H.; Finet, J-P.; Khamsi, J. *Tetrahedron Lett.* **1987**, *28*, 887). Cyclopropylamine (1.0 g, 17.5 mmol.) was added to triphenylbismuth (9.25 g, 21.0 mmol.) and cupric acetate (1.6 g, 8.75 mmol) in dichloromethane (30 mL) at room temperature under nitrogen. The mixture was stirred for 18 hours, filtered over a short plug of celite to remove any insoluble material, and purified by chromatography on a silica gel column (4 cm x 10 cm) using hexane/ethyl acetate (95/5) for elution. The fraction containing the desired product was stripped of all volatiles under vacuum to yield N-cyclopropylaniline (0.8 g). NMR (200 MHz, DMSO-d_6): δ 0.37 (m, 2H); 0.68 (m, 2H); 2.30 (m, 1H); 6.03 (br s, 1H); 6.56 (t, J=7.4 Hz, 1H); 6.70 (d, J=8.2 Hz, 2H); 7.09 (t, J=7.8 Hz, 2H)

N-Cyclopropylaniline was then be coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)-benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-cyclopropyl-N-phenylbenzamide as a yellow powder. NMR (200 MHz, DMSO-d_6): δ 0.44 (m, 2H); 0.70 (m, 2H); 0.93 (d, J=6.1 Hz, 3H); 1.01 (d, J=5.7 Hz, 3H); 1.74 (dd, J_1=7.7 Hz, J_2=11.8 Hz, 1H); 2.05 (dd, J_1=6.8 Hz, J_2=11.1 Hz, 1H); 2.39 (br d, J=10.5 Hz, 1H); 2.41-2.54 (m, 2H); 2.69 (br d, J=11.8 Hz, 1H); 2.83 (dd, J_1=6.6 Hz, J_2=13.6 Hz, 1H); 3.05-3.36 (m, 2H); 4.83 (s,1H); 5.10 (d, J=9.8 Hz, 1H); 5.17 (d, J=17.4 Hz, 1H); 5.70-5.86 (m, 1H); 6.57 (d, J=7.1 Hz, 1H); 6.63 (s, 1H); 6.65 (d, J=8.2 Hz, 1H); 7.03-7.38 (m, 10H); 9.34 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 496 (M+1, 100%), 342 (45%), 153 (90%). $[\alpha]_D^{20}$ = + 7.1° (abs. ethanol, c= 1.1). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.95 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic orange powder. Calc. for $C_{32}H_{37}N_3O_2$ HCl 1.50H_2O: C, 68.74; H, 7.39; N, 7.51; Cl, 6.34. Found: C, 68.56; H, 7.49; N, 7.26; Cl, 6.37.

EXAMPLE 19

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(3-fluorophenyl)benzamide

3-Fluoro-N-ethylaniline [NMR (DMSO-d_6, 200 MHz): δ 1.18 (t, J=7.2 Hz, 3H); 3.02 (dq, J_1=7.2 Hz, J_2=7.2 Hz, 2H); 5.86 (br m, 1H); 6.24-6.42 (m, 3H); 7.07 (q, J=7.8 Hz, 1H)] was prepared from 3-fluoroaniline and acetic anhydride, coupled with 3-((αR)-α-((2S, 5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(3-fluorophenyl)benzamide as a white solid. NMR (DMSO-d_6, 200 MHz): δ 0.92 (d, J=6 Hz, 3H); 0.96 (d, J=6 Hz, 3H); 1.05 (t, J=7 Hz, 3H); 1.7 (m, 1H); 2.05 (m, 1H); 2.3 (m, 1H); 2.5 (m, 2H); 2.7 (m, 1H); 2.9 (m, 1H); 3.2 (m, 1H); 3.9 (q, J=7 Hz, 2 H); 4.8 (s, 1H); 5.1 (d, J=10 Hz, 1H); 5.2 (d, J=16 Hz, 1H); 5.8 (m, 1H); 6.45 (d, J=8 Hz, 1H); 6.6 (s, 1H); 6.65 (d, J=8 Hz, 1H); 6.9 (d, J=8 Hz, 1H); 7.0-7.2 (m, 3H); 7.2-7.4 (m, 5H); 9.35 (s, 1H). $[\alpha]_D^{20}$ = +4.3° (abs EtOH, c=3.9). Calc. for $C_{31}H_{36}FN_3O_2$ HCl 0.5 H_2O: C, 68.06; H, 7.00; N, 7.68; Cl, 6.48. Found: C, 68.10; H, 7.04; N, 7.63; Cl, 6.42. Mass spectrum (Cl-CH_4) m/e: 502 (M+1, 39%), 501 (M, 9%), 348 (29%), 153 (100%).

EXAMPLE 20

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-propylbenzamide

2-Fluoro-N-propylaniline [NMR (DMSO-d_6, 200 MHz): δ 0.93 (t, J=7.4 Hz, 3H); 1.59 (m, 2H); 3.04 (q, 6.5 Hz, 2H); 5.33 (br m, 1H); 6.47-6.58 (m, 1H); 6.70 (t, J=8.1 Hz, 1H); 6.93-7.05 (m, 2H)] was prepared from 2-fluoroaniline and propionic anhydride, coupled with 3-((aR)-a-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-propylbenzamide as a white solid. NMR (DMSO-d_6, 200 MHz): δ 0.9-1.05 (m, 9H); 1.5 (m, 2H); 1.7 (m, 1H); 2.05 (m, 1H); 2.3 (m, 1H); 2.5 (m, 2H); 2.7 (m, 1H); 2.85 (m, 1H); 3.2 (m, 1H); 3.7 (m, 2 H); 4.8 (br s, 1H); 5.1 (d, J=10

Hz, 1H); 5.2 (d, J=16 Hz, 1H); 5.8 (m, 1H); 6.5 (d, J=8 Hz, 1H); 6.6 (s, 1H); 6.65 (d, J=8 Hz, 1H); 7.0-7.4 (m, 9H); 9.3 (s, 1H). $[\alpha]_D^{20}$ = +1.8° (abs ethanol, c=2.8). Calc. for $C_{32}H_{38}FN_3O_2$ HCl 0.25 H_2O: C, 69.05; H, 7.15; N, 7.55; Cl, 6.37. Found: C, 68.94; H, 7.19; N, 7.57; Cl, 6.41. Mass spectrum (Cl-CH_4) m/e: 516 (M+1, 93%), 515 (M, 29%), 362 (26%), 153 (100%).

EXAMPLE 21

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(2-fluorophenyl)benzamide

2-Fluoro-N-ethylaniline [NMR (DMSO-d_6, 200 MHz): δ 1.16 (t, J=7.1 Hz, 3H); 3.11 (dq, J_1=7.2 Hz, J_2=6.5 Hz, 2H); 5.30 (br m, 1H); 6.48-6.59 (m, 1H); 6.70 (t, J=8.5 Hz, 1H); 6.92-7.06 (m, 2H)] was prepared from 2-fluoroaniline and acetic anhydride, coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(2-fluorophenyl)benzamide as a light yellow wax. NMR (DMSO-d_6, 200 MHz): δ 0.9 (d, J=6 Hz, 3H); 0.95 (d, J=6 Hz, 3H); 1.1 (t, J=7 Hz, 3H); 1.7 (m, 1H); 2.1 (m, 1H); 2.3 (m, 1H); 2.5 (m, 2H); 2.7 (m, 1H); 2.85 (m, 1H); 3.8 (br m, 2H); 4.8 (br s, 1H); 5.1 (d, J=10 Hz, 1H); 5.2 (d, J=17 Hz, 1H); 5.8 (m, 1H); 6.45 (m, 1H); 6.5 (s, 1H); 6.65 (m, 1H); 7.0-7.4 (m, 9H); 9.35 (s, 1H). $[\alpha]_D^{20}$ = +3.4° (abs ethanol, c=2.04). Calc. for $C_{31}H_{36}FN_3O_2$ HCl H_2O: C, 66.95; H, 7.07; N, 7.56; Cl, 6.38. Found: C, 66.61; H, 7.14; N, 7.53; Cl, 6.40. Mass spectrum (Cl-CH_4) m/e: 502 (M+1, 89%), 501 (M, 17%), 348 (36%), 153 (100%).

EXAMPLE 22

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-propylbenzamide

3-Fluoro-N-propylaniline [NMR (DMSO-d_6, 200 MHz): δ 0.96 (t, J=7.3 Hz, 3H); 1.56 (m, 2H); 2.97 (q, 6.9 Hz, 2H); 5.93 (br m, 1H); 6.22-6.43 (m, 3H); 7.06 (q, J=7.8 Hz, 1H)] was prepared

from 3-fluoroaniline and propionic anhydride, coupled with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected and purified by the methods described in Example 3 to give (+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-propylbenzamide as a light beige solid. NMR (DMSO-d_6, 200 MHz): δ 0.9- 1.05 (m, 9H); 1.5 (m, 2H); 1.7 (m, 1H); 2.05 (m, 1H); 2.3 (m, 1H); 2.5 (m, 2H); 2.7 (m, 1H); 2.85 (m, 1H); 3.8 (m, 2H); 4.8 (s, 1H); 5.1 (d, J=10 Hz, 1H); 5.2 (d, J=16 Hz, 1H); 5.8 (m, 1H); 6.45 (d, J=8 Hz, 1H); 6.6 (s, 1H); 6.7 (d, J=8 Hz, 1H); 6.9 (d, J=8 Hz, 1H); 7.0-7.4 (m, 9H); 9.3 (s, 1H). $[\alpha]_D^{20}$ = +4.3° (abs ethanol, c=1.5). Calc. for $C_{32}H_{38}FN_3O_2$ HCl 0.75 H_2O: C, 67.95; H, 7.22; N, 7.43; Cl, 6.27. Found: C, 67.72; H, 7.19; N, 7.49; Cl, 6.30. Mass spectrum (Cl-CH_4) m/e: 516 (M+1, 100%), 515 (M, 22%), 362 (30%), 153 (73%).

EXAMPLES 23-24

The following compounds may be made by forming the appropriately substituted aniline (which is available from the parent aniline and appropriate carboxylic acid anhydride as described in Example 3), coupling with 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(tert-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotecting and purifying by the methods described in Example 3. The monohydrochloride salts may be formed using ethanolic hydrogen chloride as described in Example 3.

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-methoxyphenyl)-N-propylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-methoxyphenyl)benzamide

EXAMPLE 25

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(N-(3-fluorophenyl)-N-methylcarbamoyl)benzyl)phenyl monophosphate

(+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide (Example 7, 0.05 g, 1.03 mmol) was dissolved in dry pyridine (8 mL) under a nitrogen atmosphere. The solution was cooled to -10 °C in an ice and methanol bath. Phosphoryl chloride (394 mg) was added slowly to the cold solution. The reaction was allowed to warm to room temperature and was stirred overnight under a nitrogen atmosphere.

Water (2 mL) was added dropwise to the solution. The solution was stirred for fifteen minutes at room temperature and all volatiles were removed under reduced pressure. Ion spray mass spectrometry of the residue indicated that the crude solid is mainly the desired 3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(N-(3-fluorophenyl)-N-methylcarbamoyl)benzyl)phenyl monophosphate (ISMS M+H peak = 568.1). The phosphate may be isolated as the monoammonium salt via ion exchange chromatography.

EXAMPLE 26

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide

Crude 3-(((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(1H-benzotriazol-1-yl)methyl)-N-(3-fluorophenyl)-N-methylbenzamide was prepared from (2R,5S)-1-allyl-2,5-dimethylpiperazine (1.89 g), benzotriazole (1.39 g), and N-(3-fluorophenyl)-3-formyl-N-methylbenzamide (3.0 g) in toluene as described in Example 7.

3-Bromoanisole (4.36 g) was dissolved in dry tetrahydrofuran (40 mL), and cooled to -78 °C under nitrogen. n-Butyllithium in hexanes (9.2 mL of a 2.5M solution) was added slowly via syringe to the solution. While stirring for 25 minutes at -78 °C, the solution became white and somewhat thick. The solution was transferred via a double-ended needle to a flask containing

magnesium bromide etherate (6.02 g) in tetrahydrofuran (60 mL) and stirred for 1 hour at room temperature. The crude 3-(((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(1H-benzotriazol-1-yl)methyl)-N-(3-fluorophenyl)-N-methylbenzamide in toluene was added to the arylmagnesium bromide reagent just prepared. The solution warmed slightly during the addition and became a cloudy yellow-brown color. After stirring at room temperature for 2.5 hours, 0.5 M aqueous hydrochloric acid was added cautiously until the solution reached pH=5. The product was extracted with 100 mL of ethyl acetate and the solvent was removed under vacuum. The residue was taken up in 25 mL of 3N aqueous hydrochloric acid at room temperature. Diethyl ether was added, and the acidic aqueous layer was separated. The aqueous layer was washed a second time with diethyl ether and adjusted to pH=10 using aqueous sodium hydroxide solution. The product was extracted with ethyl acetate. The ethyl acetate portions were combined, washed with dilute sodium hydroxide solution to remove any remaining benzotriazole, washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated under reduced pressure. The crude product was purified by chromatography on a column of silica gel using 1% ethanol in dichloromethane as the eluant to give 1.71 g of (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide as a white crystalline solid in greater than 98% isomeric purity (as determined by HPLC, performed on a m-Bondapak C-18 column (125 Å, 3.9 x 300 mm, Waters Chromatography Division, Millipore Corporation, Milford, Massachusetts) using 70% methanol and 30% 0.1 M aqueous ammonium acetate at a flow rate of 1 mL/min.). NMR (200 MHz, DMSO-d6): δ 0.91 (d, J=6.0 Hz, 3H); 1.00 (d, J=6.2 Hz, 3H); 1.69 (dd, J_1=7.1 Hz, J_2= 11.0 Hz, 1H); 2.05 (dd, J_1=7.5 Hz, J_2=11.0 Hz, 1H); 2.31 (br d, J=9.3 Hz, 1H); 2.42-2.53 (m, 2H); 2.69 (br d, J=11.2 Hz, 1H); 2.85 (dd, J_1=7.0 Hz, J_2=14.1 Hz, 1H); 3.18 (dd, J_1=5.5 Hz, J_2=13.5 Hz, 1H); 3.37 (s, 3H); 3.74 (s, 3H); 4.88 (s, 1H); 5.12 (d, J=10.0 Hz, 1H); 5.18 (d, J=15.7 Hz, 1H); 5.70-5.83 (m, 1H); 6.58 (d, J=7.6 Hz, 1H); 6.70 (s, 1H); 6.84 (d, J=8.2 Hz, 1H); 6.94 (t, J=7.8 Hz, 1H); 7.02-7.14 (m, 2H); 7.18-7.34 (m, 6H); 9.31 (s, 1H). Mass spectrum (Cl-CH_4) m/e: 502 (m+1, 100%), 348 (81%), 153 (12%). $[\alpha]_D^{20}$ = + 7.73° (abs. ethanol, c= 1.1). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic light yellow powder. Calc. for $C_{31}H_{36}N_3O_2F$ HCl 0.5 H_2O: C, 68.06; H, 7.00; N, 7.68; Cl, 6.48. Found: C, 68.13; H, 7.12; N, 7.55; Cl, 6.35.

EXAMPLE 27

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide

The compound was prepared from crude 3-(((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(1H-benzotriazol-1-yl)methyl)-N-ethyl-N-(4-fluorophenyl)benzamide (Example 12, *infra*) and 3-bromoanisole by methods described in Example 7. NMR (200 MHz, DMSO-d6): δ 0.91 (d, J=6.2 Hz, 3H); 0.99 (d, J=6.3 Hz, 3H); 1.08 (t, J=7.0 Hz, 3H); 1.71 (dd, J_1=7.0 Hz, J_2=11.1 Hz, 1H); 2.03 (dd, J_1=7.1 Hz, J_2= 10.9 Hz, 1H); 2.31 (d, J=11.2 Hz, 1H); 2.40-2.57 (m, 2H); 2.67 (d, J=11.5 Hz, 1H); 2.84 (dd, J_1=6.6 Hz, J_2=13.9 Hz, 1H); 3.17 (dd, J_1=5.5 Hz, J_2= 13.9 Hz, 1H); 3.74 (s, 3H); 3.83 (q, J=7.0 Hz, 2H); 4.83 (s, 1H); 5.11 (d, J=10.2 Hz, 1H); 5.18 (d, J=16.4 Hz, 1H); 5.63-5.85 (m, 1H); 6.60 (d, J=7.4 Hz, 1H); 6.71 (s, 1H); 6.84 (d, J=8.2 Hz, 1H); 7.02-7.28 (m, 9H). Mass spectrum (Cl-CH_4) m/e: 516 (M+1, 38%), 362 (100%), 153 (16%).

EXAMPLE 28

Selected compounds of the present invention, identified below with reference to the appertaining synthesis Examples hereof, were evaluated for *in vitro* opioid receptor activity in various receptor systems, including delta receptor agonism in the mouse vas deferens (Mouse Vas Deferens ED_{50}), and mu receptor agonism in the guinea pig ileum (Guinea Pig Ileum ED_{50}).

The assay procedures used for such determinations of receptor activity are set out below.

In vitro bioassays: Vasa deferentia were removed from mice and suspended between platinum electrodes with 0.5 g of tension in organ bath chambers containing a modified Krebs' buffer of the following composition (millimolar): NaCl, 118; KCl, 4.75; $CaCl_2$, 2.6; KH_2PO_4, 1.20; $NaHCO_3$, 24.5; and glucose, 11. The buffer was saturated with 95% O_2/5% CO_2 and kept at 37 °C. Tissues were stimulated at supramaximal voltage with 10 Hz pulse trains for 400 msec.; train interval 10 seconds; and 0.5 msec pulse duration. Intact ileums (about 3 cm length) were removed from guinea pig and suspended with 1 g of tension in a bath chamber as described for the vasa

deferentia. The modified Krebs' buffer also contained $MgSO_4$ (1.20 mM). The ileums were stimulated with electrical square-wave pulses of 0.1 Hz, 0.5 msec pulse duration at supramaximal voltage. The percentage inhibition of the electrically induced muscle contractions was determined for the compounds at varying cumulative concentrations. The ED_{50} values were extrapolated from curves showing the dose concentration plotted against the response (J. A. H. Lord, A. A. Waterfield, J. Hughes, H. W. Kosterlitz, Nature 267, 495, (1977)).

Results are shown in Table A below.

Table A

In Vitro Opioid Receptor Activity[a]

Example	Delta-Receptor Mouse Vas Deferens ED_{50}(nM)	Mu-Receptor Guinea Pig Ileum ED_{50} (nM)
2	0.48 (8)	1.23 (12)
3	0.35 (12)	0.67 (8)
5	0.93 (12)	1.08 (12)
7	0.47 (8)	3.3 (8)
12	0.39 (11)	4.0 (4)
14	0.39 (4)	4.4 (4)

[a] Values are the mean of (n) number of experiments.

EXAMPLE 29

Analgesic activity was assessed by the tail pinch assay in rats (male Sprague-Dawley CD strain, weight approximately 300 g) after intravenous (i.v.) tail vein injection. A group of 6 to 8 animals was injected i.v. with compound in sterile 5% dextrose solution at a concentration of 1-5 mg/mL. Five minutes after injection, an artery clamp (Fisher Scientific Co., self-closing artery

forcep, catalog # 08-905) was placed on the tail about one inch from the tip of the tail to induce pressure nociception for a short duration (maximum of 20 seconds). The nociceptive response was judged by any sign of discomfort, such as running, squeaking, or turning around to bite the clamp. The dose-response curve was plotted for each compound. The analgesic potency (half-maximum effective dose, ED_{50}) was determined by the dose at which half of the animals do not show any nociceptive response to the artery clamp pressure within 20 seconds. Antinociceptive ED_{50} doses were 0.03 mg/kg for the compounds of Examples 7 and 12.

Pharmaceutical Formulations

In the following formulation Examples, the "Active Ingredient" may be any compound of the invention, such as a compound of formulae (I) and (II).

EXAMPLE 30

Tablet Formulations

The following formulations A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of the magnesium stearate and compression.

Formulation A

	mg/tablet	mg/tablet
(a) Active Ingredient	100	100
(b) Lactose B.P.	210	26
(c) Povidone B.P.	15	9
(d) Sodium Starch Glycollate	20	12
(e) Magnesium Stearate	5	3
	350	150

Formulation B

	mg/tablet	mg/tablet
(a) Active Ingredient	100	100

(b) Lactose	150	–
(c) Avicel PH 101	60	26
(d) Povidone B.P.	15	9
(e) Sodium Starch Glycollate	0	12
(f) Magnesium Stearate	5	3
	350	150

Formulation C

	mg/tablet
Active Ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium stearate	4
	359

The following formulations, D and E, are prepared by direct compression of the admixed ingredients.

Formulation D

	mg/tablet
Active ingredient	100
Pregelatinised Starch NF15	50
	150

Formulation E

	mg/tablet
Active ingredient	100
Lactose	150
Avicel	100
	350

Formulation F (Controlled Release Formulation)

The formulation is prepared by wet granulation of the following ingredients with a solution of povidone followed by addition of the magnesium stearate and compression.

	mg/tablet
(a) Active Ingredient	500
(b) Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c) Lactose B.P.	53
(d) Povidone B.P.C.	28
(e) Magnesium Stearate	7
	500

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

EXAMPLE 31

Capsule Formulations

Formulation A

A capsule formulation is prepared by admixing the ingredients of Formulation D in Example 62 above and filling into two-part hard gelatin capsules.

Formulation B

	mg/capsule
(a) Active Ingredient	100
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
(d) Magnesium Stearate	2
	270

Capsules are prepared by admixing the above ingredients and filling into two-part hard gelatin capsules.

Formulation C

	mg/capsule
(a) Active Ingredient	100
(b) Macrogel 4000 BP	350
	450

Capsules are prepared by melting the Macrogel 4000 BP, dispersing the active ingredient in the melt and filling the melt into two-part hard gelatin capsules.

Formulation D

	mg/capsule
Active Ingredient	100
Lecithin	100
Arachis Oil	100
	300

Capsules are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

Formulation E (Controlled Release Capsule)

The following controlled release capsule formulation is prepared by extruding ingredients (a), (b) and (c) using an extruder, followed by spheronisation of the extrudate and drying. The dried pellets are then coated with the release-controlling membrane (d) and filled into two-piece, hard gelatin capsules.

mg/capsule

(a) Active Ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Ethyl Cellulose	13
	513

EXAMPLE 32

Injectable Formulation

Formulation A

Active Ingredient	5.0 mg
Hydrochloric acid solution, 0.1M	q.s. to pH 4.0 to 7.0
Sodium hydroxide solution, 0.1M	q.s. to pH 4.0 to 7.0
Sterile Water	q.s. to 10ml

The active ingredient is dissolved in most of the water (35^{o}-40^{o}C) and the pH adjusted to between 4.0 and 7.0 using the hydrochloric acid or the sodium hydroxide as appropriate. The batch is then made up to volume with the water and filtered through a sterile micropore filter into a sterile amber glass vial 10ml and sealed with sterile closures and overseals.

Formulation B

Active Ingredient	12.5 mg
Sterile, pyrogen-free, pH 7 phosphate buffer	q.s. to 25 ml

EXAMPLE 33

Intramuscular injection

Active Ingredient	4.0 mg	
Benzyl Alcohol	0.10 g	
Glycofural 75	1.45 g	
Water for Injection	q.s. to	4.00 ml

The active ingredient is dissolved in the glycofural. The benzyl alcohol is then added and dissolved, and water added to 4 ml. The resulting mixture is filtered through a sterile micropore filter and sealed in sterile amber glass vials.

EXAMPLE 34

Syrup

Active Ingredient	0.025 g	
Sorbitol Solution	0.10 g	
Glycerol	2.00 g	
Sodium Benzoate	0.005 g	
Flavour, Peach 17.42.3169	0.0125 ml	
Purified Water	q.s. to	5.00 ml

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbitol solution and finally the flavour. The volume is made up with purified water and mixed well.

EXAMPLE 35

Suppository	mg/suppository
Active Ingredient	30
Hard Fat, BP (Witepsol H15 - Dynamit Nobel)	1970
	2000

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maxiumum. The active ingredient is sifted through a 200 mm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogeneous mix. The entire suspension is passed through a 250 mm stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.0 g of the mixture is filled into suitable, 2 ml plastic molds. The suppositories are allowed to cool to room temperature.

EXAMPLE 36

Set out below is an illustrative formulation for pessaries comprising at least one of the diarylmethyl piperazine compounds of the present invention.

Pessaries

	mg/pessary
Active Ingredient	30
Anhydrate Dextrose	490
Potato Starch	473
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

EXAMPLE 37

Set out below are additional illustrative formulations in which the compounds of the invention may be usefully employed, including formulations in the dosage forms of oral suspensions, injectable suspensions, nebulization suspensions, aerosol formulations, powder inhalation formulations, and nasal drops.

Tablet

Compound of formula (I)	25.0 mg
Lactose BP	48.5mg
Microcrystalline Cellulose BP ("Avicel pH 101")	10.0mg
Low-substituted Hydroxypropyl; Cellulose BP ("LHPC LH-11")	10mg
Sodium Starch Glycollate BP ("Explotab")	3mg
Povidone BP ("K30")	3.0mg
Magnesium Stearate BP	0.5mg
	100.0mg

Oral suspension

Compound of formula (I)	50mg
Avicel RC 591	75mg
Sucrose syrup	3.5ml
Methylhydroxybenzoate	5mg
Color	0.01%w/v
Cherry flavor	0.1%v/v
Tween 80	0.2%v/v
Water	to 5ml

Injectable suspension

Compound of formula (I)	1.5mg
Polyvinyl pyrrolidone (PVP)	170mg
Tween 80	0.2%v/v
Methylhydroxybenzoate	0.1%w/v
Water for injection	to 3ml

Capsule formulation

Compound of formula (I)	1.5mg
Starch 1500	150mg
Magnesium stearate	2.5mg

Fill the above-described formulation into a hard gelatin capsule.

Suspension for Nebulization

Compound of formula (I), sterile	1.0mg
Water for injection	to 10.0ml

Disperse the compound of formula (I) in the water for injection, as previously sterilized in a sterile container. Fill into sterile glass ampoules, 10ml/ampoule under sterile conditions, and seal each ampoule by fusion of the glass.

Aerosol Formulation

Compound of formula (I), micronized	1.0mg
Aerosol propellant	to 5.0ml

Suspend the micronized compound of formula (I) in the aerosol propellant. Fill this suspension into preformed aerosol cannisters, 5 ml/cannister under pressure, through the valve orifice.

Powder Inhalation

Compound of formula (I), micronized	1.0mg
Lactose	29.0mg

Triturate and blend the micronized compound of formula (I) with the lactose. Fill the resulting powder blend into hard gelatin capsule shells, 30mg per capsule.

Nasal Drops

Compound of formula (I)	20.0mg
Methylhydroxybenzoate	10.0mg
Water for Injection	to 10.0ml

Disperse the compound of formula (I) and the methylhydroxybenzoate in the water for injection. Fill this suspension into suitable dropper bottles, 10ml/bottle, and close by securing the dropper bottle and bottle cap.

Example 38

The following formulation may be used for microinfusion applications of formulations containing at least one compound of the invention as an active ingredient component.

Microinfusable formulation

Active ingredient	10 mg
Sodium Chloride	16 g
Hydrochloric acid solution, 0.1 M	q.s. to pH 4.0 to 7.0
Sodium hydroxide solution, 0.1 M	q.s. to pH 4.0 to 7.0
Sterile water	q.s. to 20 ml

The active ingredient and sodium chloride are dissolved in most of the water (35°-40°C) and the pH is adjusted to between 4.0 and 7.0 using the hydrochloric acid or the sodium hydroxide as appropriate. The bath then is made up to volume with the water and filtered through a sterile micropore filter into a sterile amber glass vial 20 ml and sealed with sterile closure and overseals.

Example 39

Transdermal Administration

Compositions comprising compounds of formula (I) as an active ingredient may be utilized in transdermal administration devices such as transdermal patches.

The patches bearing or otherwise containing the transdermal formulation are positioned on the body of a wearer in such manner as to remain in contact with the epidermis of the recipient for a prolonged period of time.

Such patches suitably comprise the active compound (1) in an optionally buffered, aqueous solution, (2) dissolved and/or dispersed in an adhesive, or (3) dispersed in a polymer.

A suitable concentration of the active compound is about 1% to about 35%, and preferably from about 3% to about 15%.

By way of example, the active compound may be delivered from the patch by electrotransport or iontophoresis, as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Example 40

A specific example of a transdermal formulation comprising a compound of the invention as the active ingredient is set out below.

Transdermal formulation

Active ingredient	200mg
Alcohol USP	0.1 ml
Hydroxyethyl cellulose	

The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with surface area of 10 cm^2.

Modes for Carrying Out the Invention

An advantageous mode of carrying out the invention involves the synthesis and use of preferred compounds of the invention (made by any suitable synthesis method, as for example the benzotriazole synthesis route hereinabove described), e.g., a compound selected from the group including compounds designated A, B, C, D, E, F, G and H, and pharmaceutically acceptable esters, salts, and other physiologically functional derivatives thereof, in the treatment of conditions or disorders selected from those of the group consisting of: physiological pain, diarrhea, urinary incontinence, mental illness, drug and alcohol addiction/overdose, lung edema, depression, asthma, emphysema, and apnea, cognitive disorders, and gastrointestinal disorders.

Within the foregoing, an exemplary mode of carrying out the invention with respect to the use of compounds of the invention, is the administration of same in a pharmaceutically safe and effective dose, and in a suitable dosage form, to an animal subject, e.g., a human subject, for the purpose of inducing analgesia in such animal subject.

A highly preferred compound species of the present invention is Compound G, (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide.

Industrial Applicability

Compounds of the present invention are highly selective opioid receptor binding compounds having utility as receptor-binding species, e.g., as conjugates in agonist/antagonist pairs for verifying/assaying receptor and neurotransmitter function.

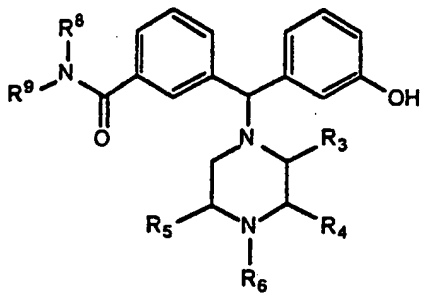
The compounds of the invention include benzhydrylpiperazine compounds useful for mediating analgesia, as well as compounds having utility in treating conditions such as drug addiction, alcohol addiction, drug overdose, mental illness, gastrointestinal disorders, urinary incontinence, diarrhea, lung edema, cough, and respiratory disorders.

A highly preferred compound within the scope of the present invention, (+)-3-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide, is a mixed delta/mu opioid agonist with substantial advantage over various known mu receptor compounds currently employed as analgesics.

CLAIMS

What we claim is :

1. A compound of formula (I) :



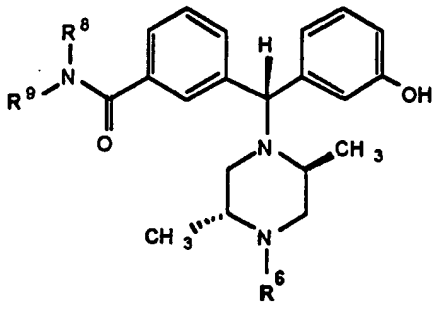
(I)

wherein :

one of R^8 and R^9 is phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, C_1-C_3 alkoxy, C_1-C_3 alkyl and trifluoromethyl, and the other of R^8 and R^9 is hydrogen or saturated C_1-C_6 hydrocarbyl or unsaturated C_3-C_6 hydrocarbyl;
one of R^3 and R^5 is methyl and the other and R^4 are both hydrogen or one is hydrogen and the other is methyl; and
R^6 is hydrogen, saturated C_1-C_6 hydrocarbyl, unsaturated C_3-C_6 hydrocarbyl or C_2-C_6 methoxyalkyl; or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

2. A compound according to claim 1, wherein R^3 and R^5 are both methyl and R^4 is hydrogen.

3. A compound according to claim 2 having the isomeric configuration of formula (II):



(II)

wherein R^8 and R^9 and R^6 are as defined in claim 1.

4. A compound according to any of the preceding claims, wherein R^6 is unsaturated C_3-C_6 hydrocarbyl.

5. A compound according to claim 4, wherein unsaturated C_3-C_6 hydrocarbyl is allyl.

6. A compound according to any of the preceding claims, wherein one of R^8 and R^9 is phenyl optionally substituted with one or more substituents selected from halogen, C_1-C_3 alkoxy and trifluoromethyl.

7. A compound according to claim 6, wherein one of R^8 and R^9 is phenyl substituted with one substituent selected from halogen, C_1-C_3 alkoxy and trifluoromethyl.

8. A compound according to either of claims 6 and 7, wherein halogen is chloro or fluoro.

9. A compound according to either of claims 6 and 7, wherein C_1-C_3 alkoxy is methoxy.

10. A compound according to claim 6, wherein phenyl is unsubstituted.

11. A compound according to any of the preceding claims, wherein the other of R^8 and R^9 is hydrogen, saturated C_1-C_6 hydrocarbyl or allyl.

12. A compound according to claim 11, wherein saturated C_1-C_6 hydrocarbyl is methyl, ethyl or propyl.

13. A compound according to claim 12, wherein propyl is n-, iso- or cyclo-propyl.

14. A compound selected from the group consisting of :

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-fluorophenyl)-N-methylbenzamide;

(+)-3-((αR)-α–((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-phenylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-chlorophenyl)-N-methylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-phenylbenzamide;

(-)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-phenylbenzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-methyl-N-(2-(trifluoromethyl)phenyl)benzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-(2,4,6-trichlorophenyl)benzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-phenyl-N-propylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-N-(4-methoxyphenyl)-N-methylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-methylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-allyl-N-phenylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(cyclopropyl)methyl-N-phenylbenzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-isopropyl-N-phenylbenzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-cyclopropyl-N-phenylbenzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-propylbenzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(3-fluorophenyl)benzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-propylbenzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(2-fluorophenyl)benzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-methoxyphenyl)-N-propylbenzamide;

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-methoxyphenyl)benzamide;

(+)-3-((αS)-α-((2S, 5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-methyl-N-phenylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxy-benzyl)-N-(4-methoxyphenyl)-N-propylbenzamide

3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(N-(3-fluorophenyl)-N-methylcarbamoyl)benzyl)phenyl monophosphate

or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

15. A compound selected from the group consisting of:

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(4-fluorophenyl)-N-methylbenzamide;

(+)-3-((αR)-α-((2S,5R)-46-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-methyl-N-phenylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-phenylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-phenyl-N-propylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-N-(4-methoxyphenyl)-N-methylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(2-fluorophenyl)-N-methylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide;

(+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide;

or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

16. (+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-(3-fluorophenyl)-N-methylbenzamide or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

17. (+)-3-((αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-(4-fluorophenyl)benzamide or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

18. A compound of formula (I) according to any of claims 1 to 17 or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof, for use in therapy.

19. The use of a compound of formula (I) according to any of claims 1 to 17 or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof for the manufacture of a medicament for the treatment or prophylaxis of a disorder selected from the following : pain, drug addiction, alcohol addiction, drug overdose, mental illness, urinary incontinence, cough, lung oedema, diarrhea, depression and cognitive, respiratory and gastro-intestinal disorders.

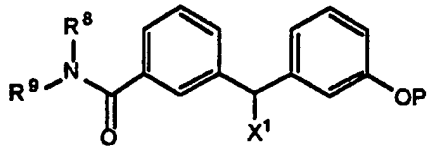
20. A pharmaceutical formulation comprising a compound of the formula (I) according to any of claims 1 to 17 or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof, and a pharmaceutically acceptable carrier therefor.

21. A method of treatment of a disorder selected from the following : pain, drug addiction, alcohol addiction, drug overdose, mental illness, urinary incontinence, cough, lung oedema, diarrhea, depression and cognitive, respiratory and gastro-intestinal disorders, which comprises the administration of an effective amount of a compound according to any of claims 1 to 17 or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

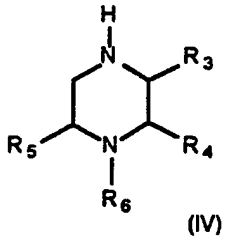
22. A method of mediating analgesia which comprises the administration of an effective amount of a compound according to any of claims 1 to 17 or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

23. A process for the preparation of a compound of formula (I) according to any of the preceding claims or a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof, said process comprising a synthesis procedure selected from the group consisting of syntheses procedures (A), (B) and (C) below:

(A) the alkylation of a piperazine of formula (IV) by an alkylating agent of formula (III),



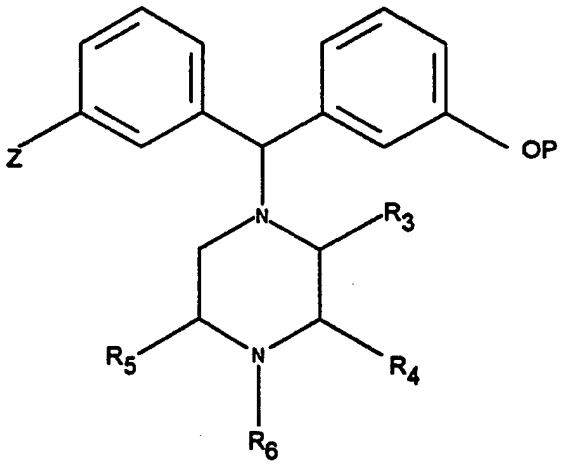
(III)



(IV)

wherein R^3 to R^6 and R^8 and R^9 are as defined in any of the preceding claims, P is hydrogen or an hydroxy-protecting group and X^1 is a leaving group; and, when R^6 is hydrogen, optionally alkylating the resulting compound of formula (I) with an alkylating agent of the formula R^6-X^1, wherein R^6 is saturated C_1-C_6 hydrocarbyl, unsaturated C_3-C_6 hydrocarbyl or C_2-C_6 methoxyalkyl and X^1 is a leaving group, or optionally alkylating the resulting compound of formula (I) by reductive amination with a C_1-C_6 aldehyde in the presence of a reducing agent;

(B) reacting a compound of formula (V),



(V)

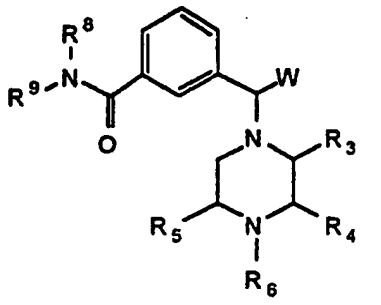
wherein R^3 to R^6 are as defined above, P is as defined above and Z is bromo, iodo or trifluoromethylsulphonyl as appropriate, with

(a) in the case where Z is bromo or iodo; an alkyl metal, optionally transmetallating the resulting metallic compound with a transition metal species to provide a different metallic compound, reacting the resulting metallic compound with carbon dioxide and converting the resulting carboxylic acid to the corresponding acid chloride, anhydride or ester, and reacting the resulting acid chloride, anhydride or ester with an amine of the formula HNR^8R^9 wherein R^8 and R^9 are as defined in any of the preceding claims, or reacting the resulting metallic compound with an aminocarbonyl chloride compound of formula $ClCONR^8R^9$, wherein R^8 and R^9 are as defined in any of the previous claims; or

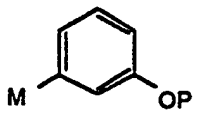
(b) in the case where Z is bromo, iodo or trifluoromethylsulphonyl; a cyanating reagent, hydrolyzing the resulting nitrile with alkali or aqueous mineral acid, converting the resulting carboxylic acid to the corresponding acid chloride, anhydride or ester, and reacting the resulting acid chloride, anhydride or ester with an amine of the formula HNR^8R^9 wherein R^8 and R^9 are as defined in any of the preceding claims; or

(c) in the case where Z is bromo, iodo or trifluoromethylsulphonyl; excess amine and carbon monoxide in the presence of a transition metal catalyst to yield a compound of formula (I), wherein R^8 and R^9 are as defined in any of the preceding claims; or

(C) reacting a compound of formula (VI), with a phenylmetallic compound of formula (VII):



(VI)



(VII)

wherein R^3 to R^6 and R^8 and R^9 are as defined in any of the preceding claims, P is hydrogen or a hydroxy-protecting group, M is a metal species and W is benzotriazolyl or trichlorotitaniumoxy;

and, when P is an hydroxy-protecting group, deprotecting the hydroxy group;

optionally converting the resulting compound of formula (I) into a pharmaceutically acceptable ether, ester or salt thereof or a physiologically functional derivative thereof.

INTERNATIONAL SEARCH REPORT

Inter. ..nal Application No
PCT/GB 94/01641

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/155 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,93 15062 (THE WELLCOME FOUNDATION LTD) 19 August 1993 cited in the application see page 17; examples 82,86	1-6, 10-15, 18-20,23
A	WO,A,93 04682 (MCNEILAB, INC) 18 March 1993 see claims	1
A	EP,A,0 133 323 (THE WELLCOME FOUNDATION LTD) 20 February 1985 see claims	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 November 1994	18. 11. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Pauwels, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/GB94/01641

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.: 21-22
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK : ALTHOUGH CLAIMS 21-22 ARE DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. onal Application No
PCT/GB 94/01641

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9315062	05-08-93	AU-B- 3457393	01-09-93
WO-A-9304682	18-03-93	AU-A- 1363392	05-04-93
		AU-A- 2659992	05-04-93
		CA-A- 2095826	12-03-93
		CA-A- 2095847	12-03-93
		EP-A- 0562049	29-09-93
		EP-A- 0563345	06-10-93
		FI-A- 932103	10-05-93
		FI-A- 932104	10-05-93
		HU-A- 64535	28-01-94
		JP-T- 6502870	31-03-94
		JP-T- 6502183	10-03-94
		WO-A- 9304684	18-03-93
EP-A-0133323	20-02-85	DE-A- 3469173	10-03-88
		JP-C- 1727360	19-01-93
		JP-B- 4015786	19-03-92
		JP-A- 60056973	02-04-85
		US-A- 4757074	12-07-88